Also provided are methods for treating a disease by degrading the function of a target protein, comprising introducing, into a cell, a chimeric protein comprising a target-protein binding domain operatively linked to a protein-degradation binding domain of a protein member of the ubiquitin-mediated protein-degradation family. For example, for a variety of proteins which, when expressed in overabundant or mutated form (e.g., an oncoprotein such as ras, or a genetic mutation, such as in the CF gene (cystic fibrosisgene) result in a known pathology, the chimeric protein of the invention may be used to therapeutically treat the disease, by way of reducing or completely eliminating, via protein degradation, the pathology causing protein. This treatment comprises fusion of a protein domain which binds the target pathology causing protein (i.e., the protein which causes the illness) with a particular protein-degradation binding domain as described herein. This chimeric protein may then be delivered to the location of the protein which causes the illness by intravenous therapy or gene therapy employing the methods described herein, or any other method well-known to one skilled in the art for delivering a protein to its binding target. As used herein, "treatment of a disease" refers to a reduction in the effects of the disease, including reducing the symptoms of the disease.

In accordance with another embodiment of the present invention, there are provided methods for diagnosing cancer, said method comprising:

detecting, in said subject, a defective sequence or mutant of SEQ ID NOs:1, 3, 5, 7, 9, 11 and 13.

In accordance with another embodiment of the present invention, there are provided diagnostic systems, preferably in kit form, comprising at least one invention nucleic acid in a suitable packaging material. The diagnostic nucleic acids are derived from the SMDP and/or SCP-encoding nucleic acids described herein. In one embodiment, for example, the diagnostic nucleic acids are derived from any of SEQ ID NOs:1, 3, 5, 7, 9, 11 and 13. Invention diagnostic systems are useful for assaying for the presence or absence of nucleic acid encoding SMDP and/or SCP in either genomic DNA or in transcribed nucleic acid (such as mRNA or cDNA) encoding SMDP and/or SCP.

A suitable diagnostic system includes at least one invention nucleic acid, preferably two or more invention nucleic acids, as a separately packaged chemical reagent(s) in an amount sufficient for at least one assay. Instructions for use of the packaged reagent are also typically included. Those of skill in the art can readily incorporate invention nucleic probes and/or primers into kit form in combination with appropriate buffers and solutions for the practice of the invention methods as described herein.

As employed herein, the phrase "packaging material" refers to one or more physical structures used to house the contents of the kit, such as invention nucleic acid probes or primers, and the like. The packaging material is constructed by well known methods, preferably to provide a sterile, contaminant-free environment. The packaging material has a label which indicates that the invention nucleic acids can be used for detecting a particular sequence encoding SMDP and/or SCP including the nucleotide sequences set forth in SEQ

ID NOs:1, 3, 5, 7, 9, 11 and 13 or mutations or deletions therein, thereby diagnosing the presence of, or a predisposition for, cancer. In addition, the packaging material contains instructions indicating how the materials within the kit are employed both to detect a particular sequence and diagnose the presence of, or a predisposition for, cancer.

The packaging materials employed herein in relation to diagnostic systems are those customarily utilized in nucleic acid-based diagnostic systems. As used herein, the term "package" refers to a solid matrix or material such as glass, plastic, paper, foil, and the like, capable of holding within fixed limits an isolated nucleic acid, oligonucleotide, or primer of the present invention. Thus, for example, a package can be a glass vial used to contain milligram quantities of a contemplated nucleic acid, oligonucleotide or primer, or it can be a microtiter plate well to which microgram quantities of a contemplated nucleic acid probe have been operatively affixed.

"Instructions for use" typically include a tangible expression describing the reagent concentration or at least one assay method parameter, such as the relative amounts of reagent and sample to be admixed, maintenance time periods for reagent/sample admixtures, temperature, buffer conditions, and the like.

All U.S. patents and all publications mentioned herein are incorporated in their entirety by reference thereto. The invention will now be described in greater detail by reference to the following non-limiting examples.

EXAMPLES

Unless otherwise stated, the present invention was performed using standard procedures, as described, for example in Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA (1982); Sambrook et al., Molecular Cloning: A Laboratory Manual (2 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA (1989); Davis et al., Basic Methods in Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1986); or Methods in Enzymology: Guide to Molecular Cloning Techniques Vol.**152**, S. L. Berger and A. R. Kimmerl Eds., Academic Press Inc., San Diego, USA (1987)).

Two-hybrid assays.

Library screening by the yeast two-hybrid method was performed herein as described (Durfee et al., 1993; Sato et al., 1995; Matsuzawa et al. 1998) using the pGilda plasmid encoding the desired amino acid region as bait, an appropriate cDNA library, and the EGY48 strain S.cerevisiae (MATa, trp1, ura3, his, leu2::plexApo6-leu2). Cells were grown in either YPD medium with 1% yeast extract, 2% polypeptone, and 2% glucose, or in Burkholder's minimal medium (BMM) fortified with appropriate amino-acids as described previously (Sato et al., 1994). Transformations were performed by a LiCl method using 0.25 mg of pJG4-5-cDNA library DNA, and 5 mg of denatured salmon sperm carrier DNA. Clones that formed on Leu deficient BMM plates containing 2% galactose/ 1% raffinose were transferred to BMM plates containing leucine and 2% glucose, and filter assays were

performed for β-galactosidase measurements as previously described.

1. Yeast two-hybrid screen of BAG-1 binding proteins to obtain cDNA encoding Siah-1α.

The mouse BAG-1 amino acid sequence was cloned into the pGilda plasmid and used as bait to screen a human Jurkat T-cell cDNA library. From an initial screen of ~1.6 X 10^7 transformants, 298 clones were identified that trans-activated the LEU2 reporter gene based on ability to grow on leucine-deficient media. Of those, 30 colonies were also positive for β-galactosidase. These 30 candidate transformants were then cured of the LexA/BAG-1 bait plasmid by growth in media containing histidine and then mated with each of 5 different indicator strains of cells containing one of following LexA bait proteins: BAG-1 (1-219), Bax (1-171), v-Ras, Fas (191-335), or Lamin-C. The mating strain was RFY206 (MATa, his3D200, leu2-3, lys2D201, ura3-52, trp1D::hisG), which had been transformed with pGilda-BAG-1 or various control proteins and selected on histidine-deficient media. This resulted in 23 clones which displayed specific two-hybrid binding interactions with BAG-1. DNA sequencing analysis revealed 4 cDNAs encoding portions of Siah-1.

2. Isolation of full-length human Siah-1α cDNAs.

To obtain the complete sequence of human Siah-1, cDNA fragments containing the 5' end of human Siah 1 were PCR-amplified from Jurkat randomly primer cDNAs by using aforward primer 5' GGGAATTCGGACTTATGGCATGTAAACA-3' (SEQ ID NO:42) containing an EcoRI site and a reverse primer 5'

TACCCAAGTTGCGAATGGA-3' (SEQ ID NO:43), based on sequences of EST database clones (NCBI ID: AA054272, AA258606, AA923663, AA418482, and AI167464). The PCR products were digested with EcoRI and BamHI, then directly subcloned into the EcoRI and SalI sites of pcI plasmid into which the cDNA derived from pJG4-5-Siah (22-298) had previously been cloned, as a BamHI - XhoI fragment. The complete human Siah-1α cDNA and amino acid sequence is set forth in SEQ ID Nos:1 and 2, respectively. The human Siah-1α sequence contains 16 N-terminal amino acids that are not present in the human Siah-1β protein.

3. Yeast two-hybrid screen of Siah-1 binding proteins to obtain cDNA encoding SIP-L and SIP-S.

Human Siah-1α cDNA encoding amino acids 22-298 of SEQ ID NO:1 (corresponding to amino acids 6-282 set forth in Nemani et al., <u>supra</u>) was cloned into the pGilda plasmid and used as a bait to screen a human embryonic brain cDNA library (Invitrogen) in EGY48 strain S.cerevisiae. From an initial screen of ~2.0 X 10^7 transformants, 322 clones were identified that trans-activated the LEU2 reporter gene based on ability to grow on leucine-deficient media. Of those, 32 colonies were also positive for ß-galactosidase. These 32 candidate transformants were then cured of the LexA/Siah-1 bait plasmid by growth in media containing histidine and then mated with each of 5 different indicator strains of cells containing one of following LexA bait proteins: Siah-1(22-298), Bax (1-171), v-Ras, Fas (191-335), or BAG-1. The mating strain was RFY206 which had been transformed with pGilda-Siah-1 or various control proteins and selected on histidine-deficient media. This resulted in 11 clones which displayed specific two-hybrid interactions with Siah-1. DNA sequencing analysis

revealed 5 cDNAs encoding portions of SIP-L, 1 cDNA encoding portions of SIP-S, 3 cDNAs encoding portions of of APC(2681-2843), and 2 cDNAs encoding portions of Siah-1. The SIP-L and SIP-S clones were sequenced and the resulting nucleotide sequences are set forth in SEQ ID Nos:3 and 5, respectively.

4. Yeast two-hybrid screen of Skp1 binding proteins to obtain cDNA encoding SAF-1 and SAD.

Human Skp1 cDNA encoding amino acids 91-163 of (Zhang et al., 1995, Cell, **82**:915-925) was cloned into the pGilda plasmid as a bait to screen a human embryonic brain cDNA library (Invtrogen) in EGY48 strain S.cerevisiae. From an initial screen of ~1.2 X 10^6 transformants, 130 clones were identified that trans-activated the LEU2 reporter gene based on ability to grow on leucine-deficient media. Of those, 36 colonies were also positive for β-galactosidase. These 36 candidate transformants were then cured of the LexA/BAG-1 bait plasmid by growth in media containing histidine and then mated with each of 5 different indicator strains of cells containing one of following LexA bait proteins: Skp1 (91-163), SIP-L, Bax (1-171), v-Ras, Fas (191-335), or Siah-1. The mating strain was RFY206 which had been transformed with pGilda-Skp1 or various control proteins and selected on histidine-deficient media. This resulted in 3 clones which displayed specific two-hybrid interactions with Skp1 and 18 clones clones which displayed specific two-hybrid interactions with both Skp1 and SIP-L. DNA sequencing analysis revealed 12 cDNAs encoding portions of SAF-1 and 9 cDNAs encoding portions of SAD. The SAF-1 and SAD clones were sequenced and the resulting nucleotide sequences are set forth in SEQ ID Nos:7 (SAF-1α), 9 (SAF-1β), and 13 (SAD).

5. Isolation of full-length SAF-2 cDNAs.

Full-length cDNA encoding a human SAF-2 protein was PCR-amplified from ZAPII Jurkat cDNA labrary (Stratagene) by using a forward primer 5'-GTGAATTCATGCAACTTGTACCTGATATAGAGTTC-3' (SEQ ID NO:44) containing an EcoRI site and a reverse primer 5'-GGACTCGAGGCTCTACAGAGGCC-3' (SEQ ID NO:45), based on human DNA sequence from clone 341E18 on chromosome 6p11.2-12.3 (AL031178). The PCR products were digested with EcoRI and XhoI, then directly subcloned into the EcoRI and XhoI sites of the plasmid pCDNA3. The corresponding plasmid was sequenced and the results are set forth in SEQ ID Nos: 11 and 12.

6. Yeast two-hybrid screen of SIP-L binding proteins.

The human SIP-L cDNA encoding full-length SIP-L was cloned into the pGilda plasmid as a bait to screen a human embryonic brain cDNA library (Invtrogen) in EGY48 strain S.cerevisiae. From an initial screen of ~1.5 X 10^7 transformants, 410 clones were identified that trans-activated the LEU2 reporter gene based on ability to grow on leucine-deficient media. Of those, 68 colonies were also positive for β-galactosidase. These 32 candidate transformants were then cured of the LexA/SIP-L bait plasmid by growth in media containing histidine and then mated with each of 32 different indicator strains of cells containing one of following LexA bait proteins: SIP-L, Bax (1-171), v-Ras, Fas (191-335), or BAG-1. The mating strain was RFY206 which had been transformed with pGilda-SIP-L or various control proteins and selected on histidine-deficient media. This resulted in 16 clones which displayed specific two-hybrid interactions with SIP-L. DNA sequencing analysis revealed 3 cDNAs encoding

portions of Skp1, 1 cDNA encoding portions of Siah-1, and 11 cDNAs encoding portions of SIP-L. These results indicate that SIP-L binds to Skp1 and Siah-1 proteins, and is able to homodimerize with SIP isoforms.

7. A cell proliferation functional assay of SIP/Siah interaction

The effects of invention SIP-L and SIP-S proteins on Siah-1-induced cell cycle arrest in 293T epithelial cancer cells was examined and the results are shown in Figure 4. Human embryonic kidney 293 cells were maintained in high-glucose DMEM medium containing 10% fetal calf serum, 1 mM L-glutamine, and antibiotics. Cells (~5 x 10^{5}) in 60 mm plates were transfected with a total of 3.0 μg of plasmid DNAs encoding Siah-1 alone or together with SIP or SIP-S by a calcium phosphate precipitation technique. After 24 hours, the cells were harvested and the number of viable and dead cells were counted using trypan blue dye exclusion assays. Efficiency of transient transfection was estimated by in situ β-galactosidase assay using a portion of the transfected cells. The transient transfection efficiency of the T293 cells was consistently 90%.

As revealed in Figure 4, over-expression of Siah-1 resulted in decreased numbers of viable cells after 24 hours, without an increase in cell death. Thus, Siah-1 suppresses proliferation of 293 cells. Co-transfection of SIP-L with Siah-1 did not substantially alter Siah-1-mediated growth suppression. In contrast, the SIP-S protein abrogated the growth suppressive effects of Siah-1, which indicates that the invention SIP-S protein affects Siah-1 intracellularly in a different manner than SIP-L.

8. **In vitro SIP:Siah-1 protein interaction assays.**

Complimentary cDNA encoding SIP-L was cloned into pGEX-4T-1 and expressed in XL-1-blue cells (Stratagene, Inc.), and affinity-purified using glutathione-Sepharose as is well-known in the art. Purified GST-fusion proteins (0.5-1.0 μg immobilized on 10-20 μl of glutathione beads) and 2.5 ul of rat reticulocyte lysates (TNT-Lysates; Promega, Inc.) containing 35S-labeled in vitro translated (IVT) Siah-1 proteins were incubated in 0.1 ml of HKMEN (10 mM HEPES [pH7.2], 142 mM KCl, 5 mM MgCl2, 2 mM EGTA, 0.1% NP-40) at 4°C for 30 minutes. The beads were washed 3X with 1 ml HKMEN solution, followed by boiling in 25 μl of Laemmli-SDS sample buffer. The eluted proteins were analyzed by SDS-PAGE (12%) and detected by fluorography. Use of equivalent amounts of intact GST-fusion proteins and successful IVT of each protein was confirmed by SDS-PAGE analysis using Coomassie staining or autoradiography, respectively.

The results are shown in Figure 5A and indicate that Siah-1 binds to SIP-L and homodimerizes in vitro.

9. **Co-immunoprecipitation Assay of SIP:Siah-1.**

Two x 10^6 293T cells in 100 mm plates were transiently transfected with 10 μg of pCDNA3-myc-SIP-L and 10 mg of pcDNA3-HA-Siah-1 (amino acids 97-298 of SEQ ID NO:2). Twenty-four hours later, cells were disrupted by sonication in 1 ml of HKMEN solution containing 0.2% NP-40, 0.1 μM PMSF, 5 μg/ml leupeptin, 1 μg/ml aprotinin, and 1 μg/ml pepstatin. After preclearing with normal mouse IgG and 10 ml protein A-agarose, immunoprecipitations were performed using 10 ml of anti-

myc antibody-conjugated sepharose (Santa Cruz) to precipitate the myc-SIP-L fusion, or an anti-IgG as a control at 4°C for 4 hours. After extensive washing in HKMEN solution, immune-complexes were analyzed by SDS-PAGE/immunoblotting using anti-HA antibody 12CA5 (Boehringer Mannheim), followed by HRPase-conjugated goat anti mouse immunoglobulin (Amersham, Inc.), and detected using an enhanced chemiluminescence (ECL) system (Amersham, Inc.).

The results are shown in Figure 5B and indicate that SIP proteins bind to Siah-1 intracellularly.

10. Yeast two-hybrid assay of Siah-1:APC binding specificity.

One µg of plasmids encoding fusion proteins of the LexA DNA-binding domain fused to Siah-1, APC(2681-2843), BAG-1, Bax, Ras, Fas, FLICE were co-tansformed into yeast strain EGY48 with 1 µg of pJG4-5 plasmid encoding fusion proteins of the B42 trans-activation domain fused to APC(2681-2843) and Siah-1. Transformed cells were grown on semi-solid media lacking leucine or containing leucine as a control which resulted in equivalent amounts of growth for all transformants. Plasmid combinations that resulted in growth on leucine-deficient media within 4 days were scored as positive (+). β-galactosidase activity of each colony was tested by filter assay and scored as blue (+) versus white (-) after 60 minutes.

The results are shown in Table 1, and indicate that APC interacts specifically by direct binding with Siah-1, and not with BAG-1, Bax, Ras, Fas nor FLICE.

Table 1: **Specific Interaction of Siah with SIP**

Lex A	B42	Leu+	β-Gal+
Siah-1	APC (2681-2843)	+	+
APC (2681-2843)	Siah-1	+	+
BAG-1	APC (2681-2843)	-	-
Bax	APC (2681-2843)	-	-
Ras	APC (2681-2843)	-	-
Fas	APC (2681-2843)	-	-
FLICE	APC (2681-2843)	-	-
empty	APC (2681-2843)	-	-

11. Yeast two-hybrid assay of Siah-1:SIP binding specificity.

One µg of plasmids encoding fusion proteins of the LexA DNA-binding domain fused to Siah-1, Siah-2, BAG-1, Bax, Ras, Fas, FLICE, and SIP-L were co-tansformed into yeast strain EGY48 with 1 µg of pJG4-5 plasmid encoding fusion proteins of the B42 trans-activation domain fused to SIP-L, SIP-S, Siah-1, Siah-2, BAG-1, Bax, and Ras. Transformed cells were grown on semi-solid media lacking leucine or containing leucine as a control which resulted in equivalent amounts of growth for all transformants. Plasmid combinations that resulted in growth on leucine-deficient media within 4 days were scored as positive (+). β-galactosidase activity of each

colony was tested by filter assay and scored as blue (+) versus white (-) after 60 minutes.

The results are shown in Table 2, and indicate that SIP proteins interact specifically by direct binding with Siah proteins. SIP-L was found to interact with Siah-1 and Siah-2, and not with BAG-1, Bax, Ras, Fas nor FLICE. SIP-S was also found to interact with Siah-1. Table G also reveals that the SIP-L homodimerization domain is within amino acids 73-228 of SIP-L (SEQ ID NO:4)

Specific Interaction of Siah with SIP

Table 2

Lex A	B42	Leu+	β-Gal+
Siah-1	SIP-L	+	+
Siah-1	SIP-S	+	+
Siah-2	SIP-L	+	+
BAG-1	SIP-L	-	-
Bax	SIP-L	-	-
Ras	SIP-L	-	-
FLICE	SIP-L	-	-
empty	SIP-L	-	-
SIP-L	Siah-1	-	+
SIP-L	Siah-2	-	+
SIP-L	BAG-1	-	-
SIP-L	Bax	-	-
SIP-L	Ras	-	-
SIP-L	SIP-L	+	+
SIP-L	SIP-S	-	-

12. Mapping of Siah-APC interaction domains.

Expression plasmids encoding fusion proteins of Siah-1α fragments corresponding to: SEQ ID NO:2 amino acids 22-298; 22-251; 22-193; 97-298; and 46-102, fused to the B-42 trans-activation domain were co-transformed into yeast EGY48 cells with a plasmid encoding a chimeric fusion protein of the Lex A DNA-binding domain fused to amino acids 2681-2843 of APC "APC(2681-2843)." Transformed cells were grown on semi-solid media lacking leucine or containing leucine as a control. Plasmid combinations that resulted in growth on leucine-deficient media within 4 days were scored as positive (+). β-

galactosidase activity for each colony was tested by filter assay and scored as blue (+) versus white (-) (β-gal) based on a 1 hour of color development.

The results are shown in Figure 3 and indicate that a region within the 47 carboxy terminal amino acids of Siah-1α (SEQ ID NO:2) is required for binding to APC.

13. Mapping of SKP-1, SIP-L, SAF-1, and SAD interaction domains.

Expression plasmids encoding fusion proteins of SAF-1α and functional fragments thereof corresponding to SEQ ID NO:8 amino acids 68-443; 80-443; and 258-443, were fused to the B-42 trans-activation domain. Likewise, expression plasmids encoding fusion proteins of SAD and functional fragments thereof corresponding to SEQ ID NO:14 amino acids 128-447; and 360-447, were fused to the B-42 trans-activation domain. These SAF-1-fragment- and SAD-fragment-B-42 fusion proteins were co-transformed into yeast EGY48 cells with a plasmid encoding a chimeric fusion protein of the Lex A DNA-binding domain fused to either SKP1, SIP-L, SAF-1, or SAD. Transformed cells were grown on semi-solid media lacking leucine or containing leucine as a control. Plasmid combinations that resulted in growth on leucine-deficient media within 4 days were scored as positive (+). β-galactosidase activity for each colony was tested by filter assay and scored as blue (+) versus white (-) (β-gal) based on a 1 hour of color development.

The results are shown in Figure 6A and 6B. Figure 6A indicates that SAF-1 interacts by direct binding to Skp1, SIP-L and SAD, but does not interact with Siah-1. A region within the SAF-1 fragment

corresponding to amino acids 80-257 of SEQ ID NO:3 is required for SIP-L interaction, whereas a region within amino acids 258-443 of SAF-1 is required for Skp1 and SAD interaction.

Figure 6B indicates that SAD interacts by direct binding to Skp1, SIP-L and SAF-1, but does not interact with Siah-1. A region within the SAD fragment corresponding to amino acids 1-127 of SEQ ID NO:14 is required for SAF-1 interaction; a region within amino acids 128-359 of SAD is required for Skp1 interaction; and a region within amino acids 360-447 of SEQ ID NO:14 is required for SIP-L interaction.

14. Effect of Siah-1 over-expression on stability of β-catenin.

293T cells were transiently transfected with a plasmid encoding myc-tagged β-catenin and either pcDNA3, pcDNA3-Siah-1, or pcDNA3-Siah-1(97-298; amino acids 97-298 of SEQ ID NO:2). Whole cell lysates were prepared, normalized for total protein content (25 µg per lane) and analyzed by SDS-PAGE/immunoblotting using an anti-Myc tag antibody.

Figure 7 indicates that expression of full-length Siah-1 abolishes, by degradation, the presence of β-catenin within cells, whereas expression of amino acids 97-298 of Siah-1 (SEQ ID NO:2) does not result in β-catenin degradation. Thus, a region within amino acids 1-96 of SEQ ID NO:2 (Siah-1α), which contains the N-terminal "Ring" domain, is required for protein degradation.

15. Demonstration of SIP-mediated degradation of a target protein, TRAF6.

An invention SIP-based method for targeted degradation of proteins was applied to the degradation TRAF proteins. The schematic in Figure 9 shows the strategy employed for targeted degradation of specific TRAF-family proteins. A chimeric protein is expressed from the plasmid pcDNA3 in which SIP-L (SEQ ID NO:3) is fused with bacterial thioredoxin containing various TRAF-binding peptides displayed on the surface of thioredoxin, as described by Brent and colleagues (Colas, et al. Nature, **380**: 548, 1996; Cohen, et al. Proc. Natl. Acad. Sci., **95**: 14272, 1998; Geyer, et al. Proc. Natl. Acad. Sci., **96**: 8562, 1999; Fabbrizio, et al. Oncogene, **18**: 4357, 1999). The TRAF-binding peptide binds to a member of the TRAF-family, and targets the TRAF-protein for ubiquitination and subsequent proteosome-dependent degradation because the SIP-region of the chimeric protein recruits ubiquitin-conjugating enzymes (E2s) to the protein complex.

Isolation of target-protein binding domain peptides that selectively bind TRAF2 and TRAF6.

A peptide aptamer library was screened by the yeast two-hybrid method to identify peptides that bind to either TRAF2 or TRAF6 using the methods described in Leo, et al. J Biol Chem, **274**:22414, 1999. TRAFs are a family of signal transducing proteins involved in cytokine receptor signaling inside cells. The sequences of the resulting TRAF-binding peptides are set forth in (Tables 3 and 4).

TABLE 3

Selected Traf 2 Aptamer Clones

Clones	(SEQ ID NO:)	SLxCIxLR motif
219	(15)	SESPGALRSGSLRCISLRIC
230	(16)	VCRGRIRSGSLRCISLRICR
221	(17)	LLRLGCIRLLMLRRGVVFRL
208	(18)	VLFLSLRFWGLNIVVMGRLL
215	(19)	CRSLGVIVGGTEAAGAPTFI
		LS motif
208	(20)	VLFLSLRFWGLNIVVMGRLL
213	(21)	WLRRGLVGVFFLLSRVMVGI
218	(22)	SLGLSVCIGRRAGGGFRGFG
237	(23)	RFALSIGVCVVVRVGICLGM
		LV motif
209	(24)	SAVLVLVYVSAALRGRGFGI
227	(25)	HGGGRGALVSVMYLCGFIRL
		Non-Consensus motif
231	(26)	RGRVIGMWVGLRCRMFLV

TABLE 4

Selected Traf 6 Aptamer Clones

Clones	(SEQ ID NO:)	WR motif
625	(27)	VDWAVYSVVWRYTTT*
631	(28)	KTSVILVWRLSLFFCLYRSL*
606	(29)	ANRCWRE*
628	(30)	EGTLSKRMWRTHN*
640	(31)	SWRDMTQSGM*
604	(32)	DVPWQRACARQ*
607	(33)	LERVARWVL*
602	(34)	VADVLVFWGYVF*
		DVxVF motif
602	(34)	VADVLVFWGYVF*
613	(35)	GDVGVFPE*
		Non-Consensus motif
603	(36)	PEMMLEGPKYCLxLxE*
609	(37)	LLYGALA*
612	(38)	GAIKFAHESCE*
616	(39)	PMAMD*
632	(40)	CEEEM*
639	(41)	ISVVHGIGSDSD*

* Termination codon

SIP-fusion Chimeric protein construction:

An invention SIP-fusion chimeric construct is generated by combining the open reading frame (ORF) of SIP$_L$, followed immediately by restriction enzyme sites allowing for subcloning of desired target-protein-binding domains (e.g. peptides or protein domains). These SIP-fusions are then transfected into mammalian cells to eliminate by protein degradation specific target proteins which bind the subcloned peptides/protein domains by recruiting them into the ubiquitin conjugating complex.

The parent SIP-vector (SIPpcDNA3.1) cassette was engineered as follows:

Oligonucleotides corresponding to the 5' and 3'end of SIP$_L$ were used in PCR to amplify the entire ORF of SIP$_L$ (SEQ ID NO:3). The forward primer contains a *Hind III* restriction site linker (5'-GATCAAGCTTATGGCTTCAGAAGAGCTACAG; (SEQ ID NO:46) restriction site is underlined) followed immediately by the SIP$_L$ (SEQ ID NO:3) start codon; the reverse primer contains an *EcoRI* restriction site and mutations in the stop codon allowing for translational readthrough (5'-GATCGAATTCtccAAATTCCGTGTCTCCTTTGGCTTG; (SEQ ID NO:47) mutated stop codon is in lowercase). The generated PCR product was then agarose gel-purified and digested with *Hind III* and *EcoRI* restriction enzymes (New England BioLabs; Beverly, MA). The product was again gel-purified before ligating into *Hind III/EcoRI* digested pcDNA3.1 expression vector (Invitrogen; Carlsbad, CA) with T4-DNA ligase (New England BioLabs). This construct was termed SIPpcDNA3.1.

For the construction of SIP-thioredoxin (Trx) peptide-aptamer fusions, clones from a peptide-aptamer library screened against Traf6 (see Table 4) were amplified by PCR with the following primers: Forward: 5'-CCTCTGAATTCCATATGAGCGATAAAATTATTCACC (SEQ ID NO:48) *EcoRI* underlined; Reverse: 5'-CATCCTCGAGTAGATGGCCAGCTAGGCCAGGTTA (SEQ ID NO:49) *Xho I* underlined.

The resulting PCR products (~350-370bp) contain the ORF of thioredoxin (Trx) with the selected peptide aptamers inserted into its active-loop. The products were then digested with *EcoRI* and *Xho I* before ligating into the *EcoRI/XhoI*-digested SIPpcDNA3.1 cassette using T4-DNA ligase. Final clone constructs were numbered and were confirmed by sequencing before using in transfection studies.

Tranfection:

HEK293T cells were transiently transfected by a lipofectamine method with various amounts (1 vs 4 µg) of pcDNA3 plasmids encoding either SIP-TR fusion protein lacking a TRAF6-binding peptide ("SIP") or SIP-TR fusion protein displaying one of the peptides shown in Table 4 above (set forth in Figure 10 as S603, S604, S606). In some cases, the proteosome inhbitor MG132 (10 µM) was added to cultures to prevent protein turnover. SIP* in Figure 10 corresponds to the control expression product of parental construct SIP pcDNA3.1

To determine the efficacy of the SIP:TRAF-binding peptide chimeric proteins, levels of TRAF6 protein were then measured two days later by immunoblotting using a anti-TRAF6-specific antiserum

(Santa Cruz Biotech, Inc.) in experiments where HEK293T cell lysates were normalized for total protein content (25 ug per lane). The cell lysates were analyzed by SDS-PAGE/immunoblotting using an enhanced chemiluminescence detection method, as described previously (Leo, et al. J Biol Chem, **274:** 22414, 1999). The results shown in the left panel of Figure 10 show that SIP-TR fusion proteins displaying TRAF6-binding peptides (S603, S604, and S613) induce a reduction in TRAF6 protein levels, with the S603 peptide representing the most potent of these.

To determine the specificity of the SIP:TRAF-binding peptide chimeric proteins, the same immunoblots were reprobed with an antiserum against SIP to demonstrate equivalent levels of production of SIP-TR fusion proteins, or with antibodies specific for TRAF2 to reveal selective degradation of TRAF6 but not TRAF2. The results shown in the right panel of Figure 10 show that addition of a proteosome inhibitor, MG132, prevents the reductions in TRAF6. Note also that TRAF2 protein is not degraded, demonstrating the specificity of the targeting approach.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

Summary of Sequences

SEQ ID NO:1 is a cDNA (and the deduced amino acid sequence) encoding a Siah 1α of the present invention.

SEQ ID NO:2 is the deduced amino acid sequence of a Siah 1α protein of the present invention encoded by SEQ ID NO:1.

SEQ ID NO:3 is a cDNA (and the deduced amino acid sequence) encoding a human SIP-L polypeptide of the present invention.

SEQ ID NO:4 is the deduced amino acid sequence of a human SIP-L protein of the present invention encoded by SEQ ID NO:3.

SEQ ID NO:5 is a cDNA (and the deduced amino acid sequence) encoding a human SIP-S polypeptide of the present invention.

SEQ ID NO:6 is the deduced amino acid sequence of a human SIP-S protein of the present invention encoded by SEQ ID NO:5.

SEQ ID NO:7 is a cDNA (and the deduced amino acid sequence) encoding a human SAF-1α polypeptide of the present invention.

SEQ ID NO:8 is the deduced amino acid sequence of a SAF-1α protein of the present invention encoded by SEQ ID NO:7.

SEQ ID NO:9 is a cDNA (and the deduced amino acid sequence) encoding a human SAF-1S polypeptide of the present invention.

SEQ ID NO:10 is the deduced amino acid sequence of a SAF-1S protein encoded by SEQ ID NO:9.

SEQ ID NO:11 is a cDNA (and the deduced amino acid sequence) encoding a human SAF-2 polypeptide of the present invention.

SEQ ID NO:12 is the deduced amino acid sequence of a SAF-2 protein encoded by SEQ ID NO:11.

SEQ ID NO:13 is a cDNA (and the deduced amino acid sequence) encoding a human SAD polypeptide of the present invention.

SEQ ID NO:14 is the deduced amino acid sequence of a SAD protein encoded by SEQ ID NO:13.

Claims

That which is claimed is:

1. Isolated nucleic acid encoding a Siah-Mediated-Degradation-Protein (SMDP) and/or SFC-Complex-Protein (SCP), or a functional fragment thereof.

2. Isolated nucleic acid encoding Siah-Mediated-Degradation-Protein (SMDP) and/or SFC-Complex-Protein (SCP), or functional fragments thereof, selected from:

(a) DNA encoding the amino acid sequence set forth in SEQ ID Nos:2, 4, 6, 8, 10, 12 or 14, or

(b) DNA that hybridizes to the DNA of (a) under moderately stringent conditions, wherein said DNA encodes biologically active SMDP and/or SCP, or

(c) DNA degenerate with respect to either (a) or (b) above, wherein said DNA encodes biologically active SMDP and/or SCP.

3. A nucleic acid according to claim 2, wherein said nucleic acid hybridizes under high stringency conditions to the SMDP and/or SCP coding portion of any of SEQ ID NOs:1, 3, 5, 7, 9, 11 and 13.

4. A nucleic acid according to claim 2, wherein the nucleotide sequence of said nucleic acid is substantially the same as set forth in any of SEQ ID NO:1, 3, 5, 7, 9, 11 and 13.

5. A nucleic acid according to claim 2, wherein the nucleotide sequence of said nucleic acid is the same as that set forth in any of SEQ ID NOs:1, 3, 5, 7, 9, 11 and 13.

6. A nucleic acid according to claim 2, wherein said nucleic acid is cDNA.

7. A vector containing the nucleic acid of claim 2.

8. Recombinant cells containing the nucleic acid of claim 2.

9. An oligonucleotide comprising at least 15 nucleotides capable of specifically hybridizing with a the nucleotide sequence set forth in any of SEQ ID NOs:1, 3, 5, 7, 9, 11 and 13.

10. An oligonucleotide according to claim 9, wherein said oligonucleotide is labeled with a detectable marker.

11. An antisense-nucleic acid capable of specifically binding to mRNA encoded by said nucleic acid according to claim 2.

12. A kit for detecting the presence of the SMDP and/or SCP cDNA sequence comprising at least one oligonucleotide according to claim 10.

13. An isolated Siah-Mediated-Degradation-Protein (SMDP) and/or SFC-Complex-Protein (SCP) characterized by having ability to bind to at least one SMDP and/or SCP.

14. A SMDP and/or SCP according to claim 13, wherein the amino acid sequence of said protein comprises substantially the same sequence as any of SEQ ID Nos:2, 4, 6, 8, 10, 12 or 14.

15. A SMDP and/or SCP according to claim 14 comprising the same amino acid sequence as set forth in any of SEQ ID Nos:2, 4, 6, 8, 10, 12 or 14.

16. A SMDP and/or SCP according to claim 13, wherein said protein is encoded by a nucleotide sequence comprising substantially the same nucleotide sequence as set forth in SEQ ID Nos:1, 3, 5, 7, 9, 11 or 13.

17. A SMDP and/or SCP according to claim 16, wherein said protein is encoded by a nucleotide sequence comprising the same sequence as set forth in SEQ ID Nos:1, 3, 5, 7, 9, 11 or 13.

18. A method for expression of a SMDP and/or SCP protein, said method comprising culturing cells of claim 8 under conditions suitable for expression of said SMDP and/or SCP.

19. An isolated anti-SMDP and/or SCP antibody having specific reactivity with a SMDP and/or SCP according to claim 13.

20. Antibody according to claim 19, wherein said antibody in a monoclonal antibody.

21. An antibody according to claim 20, wherein said antibody is a polyclonal antibody.

22. A composition comprising an amount of the antisense-nucleic acid according to claim 11 effective to inhibit expression of a human SMDP and/or SCP and an acceptable hydrophobic carrier capable of passing through a cell membrane.

23. A transgenic nonhuman mammal expressing exogenous nucleic acid encoding a SMDP and/or SCP.

24. A transgenic nonhuman mammal according to claim

23, wherein said nucleic acid encoding said SMDP and/or SCP has been mutated, and wherein the SMDP and/or SCP so expressed is not native SMDP and/or SCP.

25. A transgenic nonhuman mammal according to claim 23, wherein the transgenic nonhuman mammal is a mouse.

26. A method for identifying nucleic acids encoding a mammalian SMDP and/or SCP, said method comprising:

contacting a sample containing nucleic acids with an oligonucleotide according to claim 9, wherein said contacting is effected under high stringency hybridization conditions, and identifying compounds which hybridize thereto.

27. A method for detecting the presence of a human SMDP and/or SCP in a sample, said method comprising contacting a test sample with an antibody according to claim 19, detecting the presence of an antibody-SMDP and/or SCP complex, and therefor detecting the presence of a human SMDP and/or SCP in said test sample.

28. Single strand DNA primers for amplification of SMDP and/or SCP nucleic acid, wherein said primers comprise a nucleic acid sequence derived from the nucleic acid sequences set forth as SEQ ID NOs:1, 3, 5, 7, 9, 11 and 13.

29. A method for modulating the activity of an oncogenic protein, comprising contacting said oncogenic proteins with a substantially pure SMDP and/or SCP, or a oncogenic protein-binding fragment thereof.

30. A bioassay for evaluating whether test compounds are capable of acting as agonists or

antagonists for SMDP and/or SCP proteins, or functional fragments thereof, wherein said bioassay comprises:

(a) culturing cells containing:
DNA which expresses an SMDP and/or SCP or functional fragments thereof, wherein said culturing is carried out in the presence of at least one compound whose ability to modulate an activity of an SMDP and/or SCP is sought to be determined, wherein said activity is selected from a protein:protein binding activity or a protein degradation activity and thereafter

(b) monitoring said cells for either an increase or decrease in the level of protein:protein binding or protein degradation.

31. A method for modulating an activity mediated by a SMDP and/or SCP protein, said method comprising:
contacting said SMDP and/or SCP protein with an effective, modulating amount of said agonist or antagonist identified by claim 30.

32. The method of claim 31, wherein said modulated activity is the binding of Siah-1 to APC.

33. A method for modulating the protein degradation activity mediated by an SMDP and/or SCP protein, said method comprising:
contacting said SMDP and/or SCP protein with an effective, modulating amount of said agonist or antagonist identified by claim 30.

34. A therapeutic composition comprising a compound selected from an SMDP and/or SCP, or functional fragment

thereof, a SMDP and/or SCP modulating compound identified according to claim 30, or an anti-SMDP and/or SCP antibody; and a pharmaceutically acceptable carrier.

35. A method of treating a pathology characterized by abnormal cell proliferation or abnormal inflammation,said method comprising administering an effective amount of the composition according to claim 34.

36. A method of inducing the degradation of the function of a target protein, said method comprising:

expressing, in a cell, a chimeric protein comprising a target-protein binding domain operatively linked to a protein-degradation binding domain of a protein member of the ubiquitin-mediated protein-degradation family.

37. A method of determining the function of a target protein, said method comprising:

expressing, in a first cell, a chimeric protein comprising a target-protein binding domain operatively linked to a protein-degradation binding domain of a protein member of the ubiquitin-mediated protein-degradation family; and

comparing the phenotype of said first cell to the phenotype of a control second cell.

38. A method of identifying a nucleic acid molecule encoding a protein that modulates a cellular phenotype, said method comprising:

(a) expressing, in a cell, a chimeric nucleic acid comprising a member of a nucleic acid library fused to nucleic acid encoding a protein degradation binding domain of a protein member of the ubiquitin-mediated protein degradation family; and

(b) screening said cells for a modulator of said phenotype.

39. The method of claim 38, wherein the phenotype is selected from the group consisting of: cell proliferation, cell survival, cell death, cell secretion, and cell migration.

40. A chimeric nucleic acid identified according to claim 38.

41. A nucleic acid library comprising a plurality of chimeric nucleic acids, wherein each chimeric nucleic acid comprises an SMDP and/or SCP or functional fragment thereof.

42. The method of claim 38 wherein said nucleic acid encoding a protein degradation binding domain is selected from the group consisting of Sia-1α, SIP-L, SIP-S, SAF-1, SAF-2, and SAD, or functional fragments thereof.

43. A method for treating a disease by degrading the function of a target protein comprising:

introducing, into a cell, a chimeric protein comprising a target-protein binding domain operatively linked to a protein-degradation binding domain of a protein member of the ubiquitin-mediated protein-degradation family.

44. A chimeric protein comprising the SMDP and/or SCP of claim 13.

```
SIP-L   MASEELQKDLEEVKVLLEKATRKRVRDALTAEKSKIETEIKNKMQQKSQK  50
SIP-S   MASEELQKDLEEVKVLLEKATRKRVRDALTAEKSKIETEIKNKMQQKSQK  50

SIP-L   KAELLDNEKPAAVVAPITTGYIVKISNYGWDQSDKFVKIYITLTGVHQVP  100
SIP-S   KAELLDNEKPAAVVAPITTGYIDGISQISL--------------------  80

SIP-L   TENVQVHFTERSFDLLVKNLNGKSYSMIVNNLLKPISVEGSSKKVKTDTV  150
SIP-S   --------------------------------------------------

SIP-L   LILCRKKVENTRWDYLTQVEKECKEKEKPSYDTETDPSEGLMNVLKKIYE  200
SIP-S   --------------------------------------------------

SIP-L   DGDDDHKRTINKAWVESREKQAKGDTEF  228
SIP-S   ----------------------------
```

FIGURE 1

```
    P   P
    |   |
LYEDSGYSSFSL   SAD
SYLDSGIHSGAT   β-catenin
DRHDSGLDSMKD   IκBα
   DSGϕXS      consensus
```

FIGURE 2

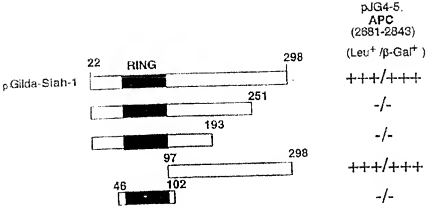

pJG4-5.
APC
(2681-2843)
(Leu+ /β-Gal+)
22
RING
298
pGilda-Siah-1
+++/+++
251
-/-
193
-/-
97
298
+++/+++
46
102
-/-

FIGURE 3

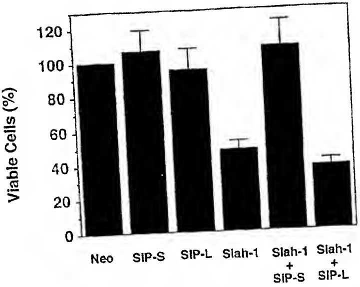
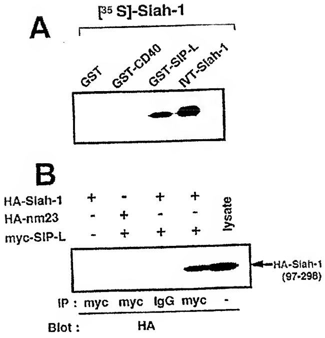
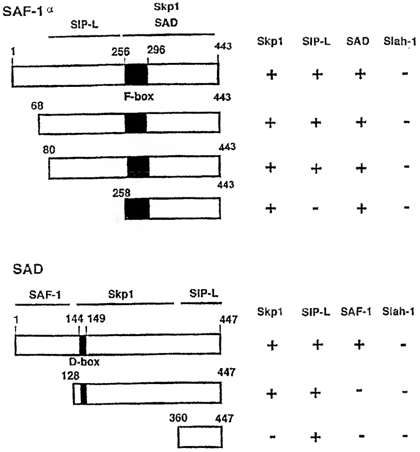

Viable Cells (%)
120
100
80
60
40
20
0
Neo
SIP-S
SIP-L
Siah-1
Siah-1 + SIP-S
Siah-1 + SIP-L

FIGURE 4



A
[35 S]-Siah-1
GST
GST-CD40
GST-SIP-L
IVT-Siah-1
B
HA-Siah-1 + - + +
HA-nm23 - + - -
myc-SIP-L - + + +
lysate
HA-Siah-1 (97-298)
IP : myc myc IgG myc -
Blot : HA

FIGURE 5


SAF-1 α
Skp1
SIP-L
SAD
1
256
296
443
F-box
68
80
258
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+ + + -
+ + + -
+ + + -
+ - + -
SAD
SAF-1
Skp1
SIP-L
1
144 149
447
D-box
128
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+ + + -
+ + - -
- + - -

FIGURE 6

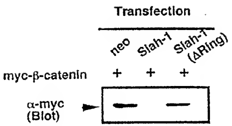

FIGURE 7

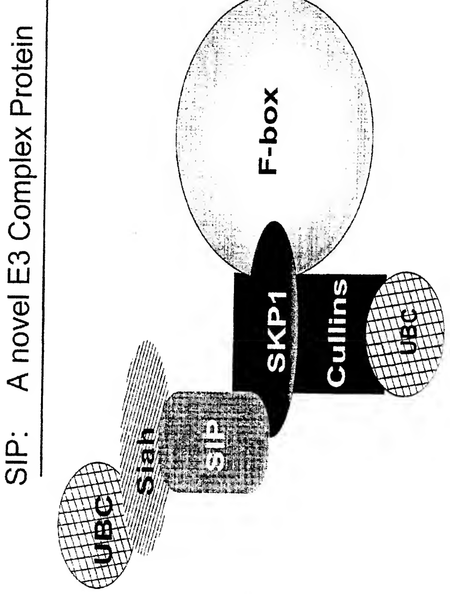
SIP: A novel E3 Complex Protein
F-box
SKP1
Cullins
UBC
SIP
Siah
UBC

FIGURE 8

Scheme for Targeted Degradation of Endogenous TRAF Proteins Using SIP and TRAF-Binding Peptides

Yeast two-hybrid peptide aptamer libraries

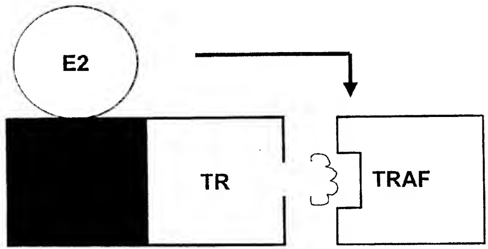

FIGURE 9

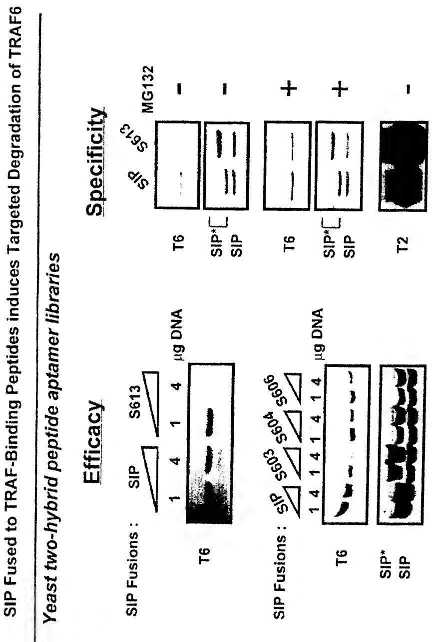
SIP Fused to TRAF-Binding Peptides induces Targeted Degradation of TRAF6
Yeast two-hybrid peptide aptamer libraries
Efficacy
SIP Fusions :
SIP
S613
1 4 1 4
µg DNA
T6
SIP Fusions :
SIP S603 S604 S606
1 4 1 4 1 4 1 4
µg DNA
T6
SIP*
SIP
Specificity
SIP S613
MG132
T6
SIP*
SIP
T6
SIP*
SIP
T2
-
-
+
+
-

FIGURE 10

SEQUENCE LISTING

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<120> Nucleic Acid Encoding Proteins Involved
  in Protein Degradation, Products and Methods Related Thereto


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<150> US 09/330,517
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cagtgtacag atcctaataa agtgcacatt cagtgtaatt ttattttttt aatatctttt     180
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tatggcatgt aaacattatt tataaagtaa gtc atg gtt ata att att ttt ctc      294
                                     Met Val Ile Ile Ile Phe Leu
                                      1               5

ctg cct cct tat gta ttt att tca gaa atg agc cgt cag act gct aca      342
Leu Pro Pro Tyr Val Phe Ile Ser Glu Met Ser Arg Gln Thr Ala Thr
        10                  15                  20

gca tta cct acc ggt acc tcg aag tgt cca cca tcc cag agg gtg cct      390
Ala Leu Pro Thr Gly Thr Ser Lys Cys Pro Pro Ser Gln Arg Val Pro
    25                  30                  35

gcc ctg act ggc aca act gca tcc aac aat gac ttg gcg agt ctt ttt      438
Ala Leu Thr Gly Thr Thr Ala Ser Asn Asn Asp Leu Ala Ser Leu Phe
40                  45                  50                  55

gag tgt cca gtc tgc ttt gac tat gtg tta ccg ccc att ctt caa tgt      486
Glu Cys Pro Val Cys Phe Asp Tyr Val Leu Pro Pro Ile Leu Gln Cys
                60                  65                  70

cag agt ggc cat ctt gtt tgt agc aac tgt cgc cca aag ctc aca tgt      534
Gln Ser Gly His Leu Val Cys Ser Asn Cys Arg Pro Lys Leu Thr Cys
            75                  80                  85
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Cys Pro Thr Cys Arg Gly Pro Leu Gly Ser Ile Arg Asn Leu Ala Met
        90                  95                  100

gag aaa gtg gct aat tca gta ctt ttc ccc tgt aaa tat gcg tct tct       630
Glu Lys Val Ala Asn Ser Val Leu Phe Pro Cys Lys Tyr Ala Ser Ser
    105                 110                 115

gga tgt gaa ata act ctg cca cac aca gaa aaa gca gac cat gaa gag       678
Gly Cys Glu Ile Thr Leu Pro His Thr Glu Lys Ala Asp His Glu Glu
120                 125                 130                 135

ctc tgt gag ttt agg cct tat tcc tgt ccg tgc cct ggt gct tcc tgt       726
Leu Cys Glu Phe Arg Pro Tyr Ser Cys Pro Cys Pro Gly Ala Ser Cys
                140                 145                 150

aaa tgg caa ggc tct ctg gat gct gta atg ccc cat ctg atg cat cag       774
Lys Trp Gln Gly Ser Leu Asp Ala Val Met Pro His Leu Met His Gln
            155                 160                 165

cat aag tcc att aca acc cta cag gga gag gat ata gtt ttt ctt gct       822
His Lys Ser Ile Thr Thr Leu Gln Gly Glu Asp Ile Val Phe Leu Ala
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Thr Asp Ile Asn Leu Pro Gly Ala Val Asp Trp Val Met Met Gln Ser
    185                 190                 195

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Cys Phe Gly Phe His Phe Met Leu Val Leu Glu Lys Gln Glu Lys Tyr
200                 205                 210                 215

gat ggt cac cag cag ttc ttc gca atc gta cag ctg ata gga aca cgc       966
Asp Gly His Gln Gln Phe Phe Ala Ile Val Gln Leu Ile Gly Thr Arg
                220                 225                 230

aag caa gct gaa aat ttt gct tac cga ctt gag cta aat ggt cat agg      1014
Lys Gln Ala Glu Asn Phe Ala Tyr Arg Leu Glu Leu Asn Gly His Arg
            235                 240                 245

cga cga ttg act tgg gaa gcg act cct cga tct att cat gaa gga att      1062
Arg Arg Leu Thr Trp Glu Ala Thr Pro Arg Ser Ile His Glu Gly Ile
        250                 255                 260

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Ala Thr Ala Ile Met Asn Ser Asp Cys Leu Val Phe Asp Thr Ser Ile
    265                 270                 275

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Ser Met Cys
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35 40 45
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50 55 60
Leu Pro Pro Ile Leu Gln Cys Gln Ser Gly His Leu Val Cys Ser Asn
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85 90 95
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115 120 125
Glu Lys Ala Asp His Glu Glu Leu Cys Glu Phe Arg Pro Tyr Ser Cys
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Pro Cys Pro Gly Ala Ser Cys Lys Trp Gln Gly Ser Leu Asp Ala Val
145 150 155 160
Met Pro His Leu Met His Gln His Lys Ser Ile Thr Thr Leu Gln Gly
165 170 175
Glu Asp Ile Val Phe Leu Ala Thr Asp Ile Asn Leu Pro Gly Ala Val
180 185 190
Asp Trp Val Met Met Gln Ser Cys Phe Gly Phe His Phe Met Leu Val
195 200 205
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Val Gln Leu Ile Gly Thr Arg Lys Gln Ala Glu Asn Phe Ala Tyr Arg
225 230 235 240
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245 250 255
Arg Ser Ile His Glu Gly Ile Ala Thr Ala Ile Met Asn Ser Asp Cys
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Leu Glu Glu Val Lys Val Leu Leu Glu Lys Ala Thr Arg Lys Arg Val
 10                 15                  20                  25

cgt gat gcc ctt aca gct gaa aaa tcc aag att gag aca gaa atc aag       147
Arg Asp Ala Leu Thr Ala Glu Lys Ser Lys Ile Glu Thr Glu Ile Lys
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Asn Lys Met Gln Gln Lys Ser Gln Lys Lys Ala Glu Leu Leu Asp Asn
            45                  50                  55

gaa aaa cca gct gct gtg gtt gct ccc att aca acg ggc tat acg gtg       243
Glu Lys Pro Ala Ala Val Val Ala Pro Ile Thr Thr Gly Tyr Thr Val
        60                  65                  70

aaa atc agt aat tat gga tgg gat cag tca gat aag ttt gtg aaa atc       291
Lys Ile Ser Asn Tyr Gly Trp Asp Gln Ser Asp Lys Phe Val Lys Ile
    75                  80                  85

tac att acc tta act gga gtt cat caa gtt ccc act gag aat gtg cag       339
Tyr Ile Thr Leu Thr Gly Val His Gln Val Pro Thr Glu Asn Val Gln
 90                 95                 100                 105

gtg cat ttc aca gag agg tca ttt gat ctt ttg gta aag aat cta aat       387
Val His Phe Thr Glu Arg Ser Phe Asp Leu Leu Val Lys Asn Leu Asn
                110                 115                 120

ggg aag agt tac tcc atg att gtg aac aat ctc ttg aaa ccc atc tct       435
Gly Lys Ser Tyr Ser Met Ile Val Asn Asn Leu Leu Lys Pro Ile Ser
            125                 130                 135

gtg gaa ggc agt tca aaa aaa gtc aag act gat aca gtt ctt ata ttg       483
Val Glu Gly Ser Ser Lys Lys Val Lys Thr Asp Thr Val Leu Ile Leu
        140                 145                 150

tgt aga aag aaa gtg gaa aac aca agg tgg gat tac ctg acc cag gtt       531
Cys Arg Lys Lys Val Glu Asn Thr Arg Trp Asp Tyr Leu Thr Gln Val
    155                 160                 165

gaa aag gag tgc aaa gaa aaa gag aag ccc tcc tat gac act gaa aca       579
Glu Lys Glu Cys Lys Glu Lys Glu Lys Pro Ser Tyr Asp Thr Glu Thr
170                 175                 180                 185

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              190                 195                 200

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        205                 210                 215

aga gag aag caa gcc aaa gga gac acg gaa ttt tgagacttta aagtcgtttt     728
Arg Glu Lys Gln Ala Lys Gly Asp Thr Glu Phe
    220                 225

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catatataaa tttgacagat agctatttac atagccttct aagtaaaggc aatcaattct     848
ccatttccta ctggaggatt tatttaaata aaatatgctt atttaaacact cctgcaaaga    908
tggttttatt agtaccctgg tcattttgtt caggaaggg ttatattgca ttctcacgtg      968
aaatataaaa agcaagtctt gcccaataaa aacgctacat tgtgtgtatt ttttgttcag    1028
ctaagaattg gaaaagtatt tgcttgcctt ttaagttact gacatcagct tccaccagtg    1088
taaaaattga gtaaaacctg aagtttttgca taaaatgcaa atcggtgcct gtgcttgaag   1148
gttgctgtag agcatctgac cccttattac cacctttaagc aatgtatatg ccatgcatta   1208
ccatgcacta attcaatcac aggtgtttct atctagattt aaatatattt gtcaatgaat    1268
gtggaataga aaatctaaac atgacaataa tagacatatc tttgtatggt accagttagt    1328
tttgccgtgg atcagatggt ttataaaagt aataaccata aagcaaaaaa taatttgaaa    1388
gcccgtctat tcctatgctc aataaagtta agtttttctt catt                     1432

<210> 4
<211> 228
<212> PRT
<213> Homo sapien

<400> 4
Met Ala Ser Glu Glu Leu Gln Lys Asp Leu Glu Glu Val Lys Val Leu
1               5                   10                  15
Leu Glu Lys Ala Thr Arg Lys Arg Val Arg Asp Ala Leu Thr Ala Glu
            20                  25                  30
Lys Ser Lys Ile Glu Thr Glu Ile Lys Asn Lys Met Gln Gln Lys Ser
        35                  40                  45
Gln Lys Lys Ala Glu Leu Leu Asp Asn Glu Lys Pro Ala Ala Val Val
    50                  55                  60
Ala Pro Ile Thr Thr Gly Tyr Thr Val Lys Ile Ser Asn Tyr Gly Trp
65                  70                  75                  80
Asp Gln Ser Asp Lys Phe Val Lys Ile Tyr Ile Thr Leu Thr Gly Val
                85                  90                  95
His Gln Val Pro Thr Glu Asn Val Gln Val His Phe Thr Glu Arg Ser
            100                 105                 110
Phe Asp Leu Leu Val Lys Asn Leu Asn Gly Lys Ser Tyr Ser Met Ile
        115                 120                 125
Val Asn Asn Leu Leu Lys Pro Ile Ser Val Glu Gly Ser Ser Lys Lys
    130                 135                 140
Val Lys Thr Asp Thr Val Leu Ile Leu Cys Arg Lys Lys Val Glu Asn
145                 150                 155                 160
Thr Arg Trp Asp Tyr Leu Thr Gln Val Glu Lys Glu Cys Lys Glu Lys
                165                 170                 175
Glu Lys Pro Ser Tyr Asp Thr Glu Thr Asp Pro Ser Glu Gly Leu Met
            180                 185                 190
Asn Val Leu Lys Lys Ile Tyr Glu Asp Gly Asp Asp Asp Met Lys Arg
        195                 200                 205
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Thr Ile Asn Lys Ala Trp Val Glu Ser Arg Glu Lys Gln Ala Lys Gly
    210                 215                 220
Asp Thr Glu Phe
225

<210> 5
<211> 1413
<212> DNA
<213> Homo sapien

<220>
<221> CDS
<222> (25)...(264)

<400> 5
ggacttcggc ctgacccagc cccc atg gct tca gaa gag cta cag aaa gat        51
                           Met Ala Ser Glu Glu Leu Gln Lys Asp
                            1               5

cta gaa gag gta aag gtg ttg ctg gaa aag gct act agg aaa aga gta       99
Leu Glu Glu Val Lys Val Leu Leu Glu Lys Ala Thr Arg Lys Arg Val
 10                 15                  20                  25

cgt gat gcc ctt aca gct gaa aaa tcc aag att gag aca gaa atc aag      147
Arg Asp Ala Leu Thr Ala Glu Lys Ser Lys Ile Glu Thr Glu Ile Lys
                30                  35                  40

aac aag atg caa cag aaa tca cag aag aaa gca gaa ctt ctt gat aat      195
Asn Lys Met Gln Gln Lys Ser Gln Lys Lys Ala Glu Leu Leu Asp Asn
            45                  50                  55

gaa aaa cca gct gct gtg gtt gct ccc att aca acg ggc tat acg gat      243
Glu Lys Pro Ala Ala Val Val Ala Pro Ile Thr Thr Gly Tyr Thr Asp
        60                  65                  70

ggg atc agt cag ata agt ttg tgaaaatcta cattacctta actggagttc         294
Gly Ile Ser Gln Ile Ser Leu
    75                  80

atcaagttcc cattgagaat gtgcaggtgc atttcacaga gaggtcattt gatcttttgg    354
taaagaatct aaatgggaag agttactcca tgattgtgaa caatctcttg aaacccatct    414
ctgtggaagg cagttcaaaa aaagtcaaga ctgatacagt tcttatattg tgtagaaaga    474
aagtggaaaa cacaaggtgg gattacctga cccaggttga aaaggagtgc aaagaaaaag    534
agaagccctc ctatgacact gaaacagatc ctagtgaggg attgatgaat gttctaaaga    594
aaatttatga agatggagac gatgatatga agcgaaccat taataaagcc tgggtggaat    654
caagagagaa gcaagccaaa ggagacacgg aattttgaga ctttaaagtc gttttgggaa    714
ctgtgatgtg atgtggaaat actgatgttt ccagtaaggg aatattggtg agctgcatat    774
ataaatttga cagatagcta tttacatagc cttctaagta aaggcaatga attctccatt    834
tcctactgga ggatttattt aaataaaata tgcttattaa acactcctgc aaagatggtt    894
ttattagtac cctggtcatt ttgttcaagg aagggttata ttgcattctc acgtgaaata    954
taaaaagcaa gtcttgccca ataaaaacgc tacattgtgt gtattttttg ttcagctaag   1014
aattggaaaa gtatttgctt gccttttaag ttactgacat cagcttccac cagtgtaaaa   1074
attgagtaaa acctgaagtt ttgcataaaa tgcaaatcgg tgcctgtgct tgaaggttgc   1134
tgtagagcat ctgacccctt attaccacct taagcaatgt atatgctatg cattaccatg   1194
cactaattca atcacaggtg tttctatcta gatttaaata tatttgtcaa tgaatgtgga   1254
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atagaaaatc taaacatgac aataatagac atatctttgt atggtaccag ttagttttgc    1314
cgtggatcac atggtttata aaagtaataa ccataaagca aaaaataatt tgaaagcccg    1374
tctattccta tgttcaataa agttaagttt ttcttcatt                           1413

<210> 6
<211> 80
<212> PRT
<213> Homo sapien

<400> 6
Met Ala Ser Glu Glu Leu Gln Lys Asp Leu Glu Glu Val Lys Val Leu
 1               5                  10                  15
Leu Glu Lys Ala Thr Arg Lys Arg Val Arg Asp Ala Leu Thr Ala Glu
            20                  25                  30
Lys Ser Lys Ile Glu Thr Glu Ile Lys Asn Lys Met Gln Gln Lys Ser
        35                  40                  45
Gln Lys Lys Ala Glu Leu Leu Asp Asn Glu Lys Pro Ala Ala Val Val
    50                  55                  60
Ala Pro Ile Thr Thr Gly Tyr Thr Asp Gly Ile Ser Gln Ile Ser Leu
65                  70                  75                  80

<210> 7
<211> 1673
<212> DNA
<213> Homo sapien

<220>
<221> CDS
<222> (61)...(1389)

<400> 7
ccggagggtg caggcgacgg gaagcgcggg tggtcggctg gggtccggct cctggagaac      60
atg gcc cgg cct ccc ggg ggc tct ggt ccc ctc ctc gat tca gag cat       108
Met Ala Arg Pro Pro Gly Gly Ser Gly Pro Leu Leu Asp Ser Glu His
 1               5                  10                  15

tct tca ctc cag aat aat gag caa ccc tct ttg gcc acc agc tcc aat       156
Ser Ser Leu Gln Asn Asn Glu Gln Pro Ser Leu Ala Thr Ser Ser Asn
            20                  25                  30

cag act agc atg cag gat gaa caa cca agt gat tca ttc caa gga cag       204
Gln Thr Ser Met Gln Asp Glu Gln Pro Ser Asp Ser Phe Gln Gly Gln
        35                  40                  45

gca gcc cag tct ggt gtt tgg aat gac gac agt atg tta ggg cct agt       252
Ala Ala Gln Ser Gly Val Trp Asn Asp Asp Ser Met Leu Gly Pro Ser
    50                  55                  60

caa aat ttt gaa gct gag tca att caa gat aat gcg cat atg gca gag       300
Gln Asn Phe Glu Ala Glu Ser Ile Gln Asp Asn Ala His Met Ala Glu
 65                  70                  75                  80

ggc aca ggt ttc tat ccc tca gaa ccc atg ctc tgt agt gaa tcg gtg       348
Gly Thr Gly Phe Tyr Pro Ser Glu Pro Met Leu Cys Ser Glu Ser Val
                85                  90                  95
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gaa ggg caa gtg cca cat tca tta gag acc ttg tat caa tca gct gac 396
Glu Gly Gln Val Pro His Ser Leu Glu Thr Leu Tyr Gln Ser Ala Asp
100 105 110

tgt tct gat gcc aat gat gcc ttg ata gtg ttg ata cat ctt ctc atg 444
Cys Ser Asp Ala Asn Asp Ala Leu Ile Val Leu Ile His Leu Leu Met
115 120 125

ttg gag tca ggt tac ata cct cag ggc acc gaa gcc aaa gca ctg tcc 492
Leu Glu Ser Gly Tyr Ile Pro Gln Gly Thr Glu Ala Lys Ala Leu Ser
130 135 140

atg ccg gag aag tgg aag ttg agc ggg gtg tat aag ctg cag tac atg 540
Met Pro Glu Lys Trp Lys Leu Ser Gly Val Tyr Lys Leu Gln Tyr Met
145 150 155 160

cat cct ctc tgc gag ggc agc tcc gct act ctc acc tgt gtg cct ttg 588
His Pro Leu Cys Glu Gly Ser Ser Ala Thr Leu Thr Cys Val Pro Leu
165 170 175

gga aac ctg att gtt gta aat gct aca cta aaa atc aac aat gag att 636
Gly Asn Leu Ile Val Val Asn Ala Thr Leu Lys Ile Asn Asn Glu Ile
180 185 190

aga agt gtg aaa aga ttg cag ctg cta cca aaa tct ttt att tgc aaa 684
Arg Ser Val Lys Arg Leu Gln Leu Leu Pro Lys Ser Phe Ile Cys Lys
195 200 205

gag aaa cta ggg gaa aat gta gcc aac ata tac aaa gat ctt cag aaa 732
Glu Lys Leu Gly Glu Asn Val Ala Asn Ile Tyr Lys Asp Leu Gln Lys
210 215 220

ctc tct cgc ctc ttt aaa gac cag ctg gtg tat cct ctt ctg gct ttt 780
Leu Ser Arg Leu Phe Lys Asp Gln Leu Val Tyr Pro Leu Leu Ala Phe
225 230 235 240

acc cga caa gca ctg aac cta cca gat gta ttt ggg ttg gtc gtc ctc 828
Thr Arg Gln Ala Leu Asn Leu Pro Asp Val Phe Gly Leu Val Val Leu
245 250 255

cca ttg gag ctg aaa cta cgg atc ttc cga ctt ctg gat gtt cgt tcc 876
Pro Leu Glu Leu Lys Leu Arg Ile Phe Arg Leu Leu Asp Val Arg Ser
260 265 270

gtc ttg tct ttg tct gcg gtt tgt cgt gac ctc ttt act gct tca aat 924
Val Leu Ser Leu Ser Ala Val Cys Arg Asp Leu Phe Thr Ala Ser Asn
275 280 285

gac cca ctc ctg tgg agg ttt tta tat ctg cgt gat ttt cga gac aat 972
Asp Pro Leu Leu Trp Arg Phe Leu Tyr Leu Arg Asp Phe Arg Asp Asn
290 295 300

act gtc aga gtt caa gac aca gat tgg aaa gaa ctg tac agg aag agg 1020
Thr Val Arg Val Gln Asp Thr Asp Trp Lys Glu Leu Tyr Arg Lys Arg

305 310 315 320

cac ata caa aga aaa gaa tcc ccg aaa ggg cgg ttt gtg atg ctc ctg 1068
His Ile Gln Arg Lys Glu Ser Pro Lys Gly Arg Phe Val Met Leu Leu
325 330 335

cca tcg tca act cac acc att cca ttc tat ccc aac ccc ttg cac cct 1116
Pro Ser Ser Thr His Thr Ile Pro Phe Tyr Pro Asn Pro Leu His Pro
340 345 350

agg cca ttt cct agc tcc cgc ctt cct cca gga att atc ggg ggt gaa 1164
Arg Pro Phe Pro Ser Ser Arg Leu Pro Pro Gly Ile Ile Gly Gly Glu
355 360 365

tat gac caa aga cca aca ctt ccc tat gtt gga gac cca atc agt tca 1212
Tyr Asp Gln Arg Pro Thr Leu Pro Tyr Val Gly Asp Pro Ile Ser Ser
370 375 380

ctc att cct ggt cct ggg gag acg ccc agc cag ttt cct cca ctc aga 1260
Leu Ile Pro Gly Pro Gly Glu Thr Pro Ser Gln Phe Pro Pro Leu Arg
385 390 395 400

cca cgc ttt gat cca gtt ggc cca ctt cca gga cct aac ccc att ttg 1308
Pro Arg Phe Asp Pro Val Gly Pro Leu Pro Gly Pro Asn Pro Ile Leu
405 410 415

cca ggg cga ggc ggc ccc aat gac aga ttt ccc ttt aga ccc agc agg 1356
Pro Gly Arg Gly Gly Pro Asn Asp Arg Phe Pro Phe Arg Pro Ser Arg
420 425 430

ggt cgg cca act gat ggc cgg ctg tca ttc atg tgattgattt gtaatttcat 1409
Gly Arg Pro Thr Asp Gly Arg Leu Ser Phe Met
435 440

ttctggagct ccatttgttt ttgtttctaa actaaagatg tcaactcctt ggggtgctga 1469
tctcgagtgt tattttctga ttgtggtgtt gagagttgca ctcccagaaa ccttttaaga 1529
gatacattta tagccctagg ggtggtatga cccaaaggtt cctctgtgac aaggttggcc 1589
ttgggaatag ttggctgcca atctccctgc tcttggttct cctctagatt gaagtttgtt 1649
ttctgatgct gttcttacca gatt 1673

<210> 8
<211> 443
<212> PRT
<213> Homo sapien

<400> 8
Met Ala Arg Pro Pro Gly Gly Ser Gly Pro Leu Leu Asp Ser Glu His
1 5 10 15
Ser Ser Leu Gln Asn Asn Glu Gln Pro Ser Leu Ala Thr Ser Ser Asn
20 25 30
Gln Thr Ser Met Gln Asp Glu Gln Pro Ser Asp Ser Phe Gln Gly Gln
35 40 45
Ala Ala Gln Ser Gly Val Trp Asn Asp Asp Ser Met Leu Gly Pro Ser
50 55 60
Gln Asn Phe Glu Ala Glu Ser Ile Gln Asp Asn Ala His Met Ala Glu

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65                  70                  75                  80
Gly Thr Gly Phe Tyr Pro Ser Glu Pro Met Leu Cys Ser Glu Ser Val
                85                  90                  95
Glu Gly Gln Val Pro His Ser Leu Glu Thr Leu Tyr Gln Ser Ala Asp
            100                 105                 110
Cys Ser Asp Ala Asn Asp Ala Leu Ile Val Leu Ile His Leu Leu Met
        115                 120                 125
Leu Glu Ser Gly Tyr Ile Pro Gln Gly Thr Glu Ala Lys Ala Leu Ser
    130                 135                 140
Met Pro Glu Lys Trp Lys Leu Ser Gly Val Tyr Lys Leu Gln Tyr Met
145                 150                 155                 160
His Pro Leu Cys Glu Gly Ser Ser Ala Thr Leu Thr Cys Val Pro Leu
                165                 170                 175
Gly Asn Leu Ile Val Val Asn Ala Thr Leu Lys Ile Asn Asn Glu Ile
            180                 185                 190
Arg Ser Val Lys Arg Leu Gln Leu Leu Pro Lys Ser Phe Ile Cys Lys
        195                 200                 205
Glu Lys Leu Gly Glu Asn Val Ala Asn Ile Tyr Lys Asp Leu Glu Lys
    210                 215                 220
Leu Ser Arg Leu Phe Lys Asp Gln Leu Val Tyr Pro Leu Leu Ala Phe
225                 230                 235                 240
Thr Arg Gln Ala Leu Asn Leu Pro Asp Val Phe Gly Leu Val Val Leu
                245                 250                 255
Pro Leu Glu Leu Lys Leu Arg Ile Phe Arg Leu Leu Asp Val Arg Ser
            260                 265                 270
Val Leu Ser Leu Ser Ala Val Cys Arg Asp Leu Phe Thr Ala Ser Asn
        275                 280                 285
Asp Pro Leu Leu Trp Arg Phe Leu Tyr Leu Arg Asp Phe Arg Asp Asn
    290                 295                 300
Thr Val Arg Val Gln Asp Thr Asp Trp Lys Glu Leu Tyr Arg Lys Arg
305                 310                 315                 320
His Ile Gln Arg Lys Glu Ser Pro Lys Gly Arg Phe Val Met Leu Leu
                325                 330                 335
Pro Ser Ser Thr His Thr Ile Pro Phe Tyr Pro Asn Pro Leu His Pro
            340                 345                 350
Arg Pro Phe Pro Ser Ser Arg Leu Pro Pro Gly Ile Ile Gly Gly Glu
        355                 360                 365
Tyr Asp Gln Arg Pro Thr Leu Pro Tyr Val Gly Asp Pro Ile Ser Ser
    370                 375                 380
Leu Ile Pro Gly Pro Gly Glu Thr Pro Ser Gln Phe Pro Pro Leu Arg
385                 390                 395                 400
Pro Arg Phe Asp Pro Val Gly Pro Leu Pro Gly Pro Asn Pro Ile Leu
                405                 410                 415
Pro Gly Arg Gly Gly Pro Asn Asp Arg Phe Pro Phe Arg Pro Ser Arg
            420                 425                 430
Gly Arg Pro Thr Asp Gly Arg Leu Ser Phe Met
        435                 440
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<210> 9
<211> 1897
<212> DNA
<213> Homo sapien

<220>
<221> CDS

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<222> (43)...(1608)

<400> 9
gccgcctccg ggtccaggcc cctcgggccg cctgccgccg tc atg agg ctg cgg        54
                                               Met Arg Leu Arg
                                                1

gtg cgg ctt ctg aag cgg acc tgg ccg ctg gag gtg ccc gag acg gag      102
Val Arg Leu Leu Lys Arg Thr Trp Pro Leu Glu Val Pro Glu Thr Glu
 5                  10                  15                  20

ccg acg ctg ggg cat ctg cgc tcg cac ctg agg cag tcc ctg ctg tgc      150
Pro Thr Leu Gly His Leu Arg Ser His Leu Arg Gln Ser Leu Leu Cys
                25                  30                  35

acc tgg ggc tac agt tct aat acc cga ttt aca att aca ttg aac tac      198
Thr Trp Gly Tyr Ser Ser Asn Thr Arg Phe Thr Ile Thr Leu Asn Tyr
            40                  45                  50

aag gat ccc ctc act gga gat gaa gag acc ttg gct tca tat ggg att      246
Lys Asp Pro Leu Thr Gly Asp Glu Glu Thr Leu Ala Ser Tyr Gly Ile
        55                  60                  65

gtt tct ggg gac ttg ata tgt ttg att ctt caa gat gac att cca gcg      294
Val Ser Gly Asp Leu Ile Cys Leu Ile Leu Gln Asp Asp Ile Pro Ala
    70                  75                  80

cct aat ata cct tca tcc aca gat tca gag cat tct tca ctc cag aat      342
Pro Asn Ile Pro Ser Ser Thr Asp Ser Glu His Ser Ser Leu Gln Asn
85                  90                  95                 100

aat gag caa ccc tct ttg gcc acc agc tcc aat cag act agc atg cag      390
Asn Glu Gln Pro Ser Leu Ala Thr Ser Ser Asn Gln Thr Ser Met Gln
                105                 110                 115

gat gaa caa cca agt gat tca ttc caa gga cag gca gcc cag tct ggt      438
Asp Glu Gln Pro Ser Asp Ser Phe Gln Gly Gln Ala Ala Gln Ser Gly
            120                 125                 130

gtt tgg aat gac gac agt atg tta ggg cct agt caa aat ttt gaa gct      486
Val Trp Asn Asp Asp Ser Met Leu Gly Pro Ser Gln Asn Phe Glu Ala
        135                 140                 145

gag tca att caa gat aat gcg cat atg gca gag ggc aca ggt ttc tat      534
Glu Ser Ile Gln Asp Asn Ala His Met Ala Glu Gly Thr Gly Phe Tyr
    150                 155                 160

ccc tca gaa ccc atg ctc tgt agt gaa tcg gtg gaa ggg caa gtg cca      582
Pro Ser Glu Pro Met Leu Cys Ser Glu Ser Val Glu Gly Gln Val Pro
165                 170                 175                 180

cat tca tta gag acc ttg tat caa tca gct gac tgt tct gat gct aat      630
His Ser Leu Glu Thr Leu Tyr Gln Ser Ala Asp Cys Ser Asp Ala Asn
                185                 190                 195
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gat gcc ttg ata gtg ttg ata cat ctt ctc atg ttg gag tca ggt tac      678
Asp Ala Leu Ile Val Leu Ile His Leu Leu Met Leu Glu Ser Gly Tyr
        200                 205                 210

ata cct cag ggc acc gaa gcc aaa gca ctg tcc atg ccg gag aag tgg      726
Ile Pro Gln Gly Thr Glu Ala Lys Ala Leu Ser Met Pro Glu Lys Trp
        215                 220                 225

aag ttg agc ggg gtg tat aag ctg cag tac atg cat cct ctc tgc gag      774
Lys Leu Ser Gly Val Tyr Lys Leu Gln Tyr Met His Pro Leu Cys Glu
    230                 235                 240

ggc agc tcc gct act ctc acc tgt gtg cct ttg gga aac ctg att gtt      822
Gly Ser Ser Ala Thr Leu Thr Cys Val Pro Leu Gly Asn Leu Ile Val
245                 250                 255                 260

gta aat gct aca cta aaa atc aac aat gag att aga agt gtg aaa aga      870
Val Asn Ala Thr Leu Lys Ile Asn Asn Glu Ile Arg Ser Val Lys Arg
                265                 270                 275

ttg cag ctg cta cca aaa tct ttt att tgc aaa gag aaa cta ggg gaa      918
Leu Gln Leu Leu Pro Lys Ser Phe Ile Cys Lys Glu Lys Leu Gly Glu
            280                 285                 290

aat gta gct aac ata tac aaa gat ctt cag aaa ctc tct cgc ctc ttt      966
Asn Val Ala Asn Ile Tyr Lys Asp Leu Gln Lys Leu Ser Arg Leu Phe
        295                 300                 305

aaa gac cag ctg gtg tat cct ctt ctg gct ttt acc cga caa gca ctg     1014
Lys Asp Gln Leu Val Tyr Pro Leu Leu Ala Phe Thr Arg Gln Ala Leu
    310                 315                 320

aac cta cca gat gta ttt ggg ttg gtc gtc ctc cca ttg gaa ctg aaa     1062
Asn Leu Pro Asp Val Phe Gly Leu Val Val Leu Pro Leu Glu Leu Lys
325                 330                 335                 340

cta cgg atc ttc cga ctt ctg gat gtt cgt tcc gtc ttg tct ttg tct     1110
Leu Arg Ile Phe Arg Leu Leu Asp Val Arg Ser Val Leu Ser Leu Ser
                345                 350                 355

gcg gtt tgt cgt gac ctc ttt act gct tca aat gac cca ctc ctg tgg     1158
Ala Val Cys Arg Asp Leu Phe Thr Ala Ser Asn Asp Pro Leu Leu Trp
            360                 365                 370

agg ttt tta tat ctg cgt gat ttt cga gac aat act gtc aga gtt caa     1206
Arg Phe Leu Tyr Leu Arg Asp Phe Arg Asp Asn Thr Val Arg Val Gln
        375                 380                 385

gac aca gat tgg aaa gaa ctg tac agg aag agg cac ata caa aga aaa     1254
Asp Thr Asp Trp Lys Glu Leu Tyr Arg Lys Arg His Ile Gln Arg Lys
    390                 395                 400

gaa tcc ccg aaa ggg cgg ttt gtg atg ctc ctg cca tcg tca act cac     1302
Glu Ser Pro Lys Gly Arg Phe Val Met Leu Leu Pro Ser Ser Thr His
405                 410                 415                 420
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acc att cca ttc tat ccc aac ccc ttg cat cct agg cca ttt cct agc 1350
Thr Ile Pro Phe Tyr Pro Asn Pro Leu His Pro Arg Pro Phe Pro Ser
425 430 435

tcc cgc ctt cct cca gga att atc ggg ggt gaa tat gac caa aga cca 1398
Ser Arg Leu Pro Pro Gly Ile Ile Gly Gly Glu Tyr Asp Gln Arg Pro
440 445 450

aca ctt ccc tat gtt gga gac cca atc agt tca ctc att cct ggt cct 1446
Thr Leu Pro Tyr Val Gly Asp Pro Ile Ser Ser Leu Ile Pro Gly Pro
455 460 465

ggg gag acg ccc agc cag ttt cct cca ctg aga cca cgc ttt gat cca 1494
Gly Glu Thr Pro Ser Gln Phe Pro Pro Leu Arg Pro Arg Phe Asp Pro
470 475 480

gtt ggc cca ctt cca gga cct aac ccc atc ttg cca ggg cga ggc ggc 1542
Val Gly Pro Leu Pro Gly Pro Asn Pro Ile Leu Pro Gly Arg Gly Gly
485 490 495 500

ccc aat gac aga ttt ccc ttt aga ccc agc agg ggt cgg cca act gat 1590
Pro Asn Asp Arg Phe Pro Phe Arg Pro Ser Arg Gly Arg Pro Thr Asp
505 510 515

ggc cgg ctg tca ttc atg tgattgattt gtaatttcat ttctggagct 1638
Gly Arg Leu Ser Phe Met
520

ccatttgttt ttgtttctaa actacagatg tcaactcctt ggggtgctga tctcgagtgt 1698
tatttttctga ttgtggtgtt gagagttgca ctcccagaaa ccttttaaga gatacattta 1758
tagccctagg ggtggtatga cccaaaggtt cctctgtgac aaggttggcc ttgggaatag 1818
ttggctgcca atctccctgc tcttggttct cctctagatt gaagtttgtt tttgatgct 1878
gttcttacca gatt 1892

<210> 10
<211> 522
<212> PRT
<213> Homo sapien

<400> 10
Met Arg Leu Arg Val Arg Leu Leu Lys Arg Thr Trp Pro Leu Glu Val
1 5 10 15
Pro Glu Thr Glu Pro Thr Leu Gly His Leu Arg Ser His Leu Arg Gln
20 25 30
Ser Leu Leu Cys Thr Trp Gly Tyr Ser Ser Asn Thr Arg Phe Thr Ile
35 40 45
Thr Leu Asn Tyr Lys Asp Pro Leu Thr Gly Asp Glu Glu Thr Leu Ala
50 55 60
Ser Tyr Gly Ile Val Ser Gly Asp Leu Ile Cys Leu Ile Leu Gln Asp
65 70 75 80
Asp Ile Pro Ala Pro Asn Ile Pro Ser Ser Thr Asp Ser Glu His Ser
85 90 95
Ser Leu Gln Asn Asn Glu Gln Pro Ser Leu Ala Thr Ser Ser Asn Gln
100 105 110

Thr Ser Met Gln Asp Glu Gln Pro Ser Asp Ser Phe Gln Gly Gln Ala
115 120 125
Ala Gln Ser Gly Val Trp Asn Asp Asp Ser Met Leu Gly Pro Ser Gln
130 135 140
Asn Phe Glu Ala Glu Ser Ile Gln Asp Asn Ala His Met Ala Glu Gly
145 150 155 160
Thr Gly Phe Tyr Pro Ser Glu Pro Met Leu Cys Ser Glu Ser Val Glu
165 170 175
Gly Gln Val Pro His Ser Leu Glu Thr Leu Tyr Gln Ser Ala Asp Cys
180 185 190
Ser Asp Ala Asn Asp Ala Leu Ile Val Leu Ile His Leu Leu Met Leu
195 200 205
Glu Ser Gly Tyr Ile Pro Gln Gly Thr Glu Ala Lys Ala Leu Ser Met
210 215 220
Pro Glu Lys Trp Lys Leu Ser Gly Val Tyr Lys Leu Gln Tyr Met His
225 230 235 240
Pro Leu Cys Glu Gly Ser Ser Ala Thr Leu Thr Cys Val Pro Leu Gly
245 250 255
Asn Leu Ile Val Val Asn Ala Thr Leu Lys Ile Asn Asn Glu Ile Arg
260 265 270
Ser Val Lys Arg Leu Gln Leu Leu Pro Lys Ser Phe Ile Cys Lys Glu
275 280 285
Lys Leu Gly Glu Asn Val Ala Asn Ile Tyr Lys Asp Leu Gln Lys Leu
290 295 300
Ser Arg Leu Phe Lys Asp Gln Leu Val Tyr Pro Leu Leu Ala Phe Thr
305 310 315 320
Arg Gln Ala Leu Asn Leu Pro Asp Val Phe Gly Leu Val Val Leu Pro
325 330 335
Leu Glu Leu Lys Leu Arg Ile Phe Arg Leu Leu Asp Val Arg Ser Val
340 345 350
Leu Ser Leu Ser Ala Val Cys Arg Asp Leu Phe Thr Ala Ser Asn Asp
355 360 365
Pro Leu Leu Trp Arg Phe Leu Tyr Leu Arg Asp Phe Arg Asp Asn Thr
370 375 380
Val Arg Val Gln Asp Thr Asp Trp Lys Glu Leu Tyr Arg Lys Arg His
385 390 395 400
Ile Gln Arg Lys Glu Ser Pro Lys Gly Arg Phe Val Met Leu Leu Pro
405 410 415
Ser Ser Thr His Thr Ile Pro Phe Tyr Pro Asn Pro Leu His Pro Arg
420 425 430
Pro Phe Pro Ser Ser Arg Leu Pro Pro Gly Ile Ile Gly Gly Glu Tyr
435 440 445
Asp Gln Arg Pro Thr Leu Pro Tyr Val Gly Asp Pro Ile Ser Ser Leu
450 455 460
Ile Pro Gly Pro Gly Glu Thr Pro Ser Gln Phe Pro Pro Leu Arg Pro
465 470 475 480
Arg Phe Asp Pro Val Gly Pro Leu Pro Gly Pro Asn Pro Ile Leu Pro
485 490 495
Gly Arg Gly Gly Pro Asn Asp Arg Phe Pro Phe Arg Pro Ser Arg Gly
500 505 510
Arg Pro Thr Asp Gly Arg Leu Ser Phe Met
515 520

<210> 11
<211> 1075

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<212> DNA
<213> Homo sapien

<220>
<221> CDS
<222> (52)...(1032)

<400> 11
gctaatttag ctttatttct tcttttagcc atcaagtttt atcgtagggc t atg caa      57
                                                         Met Gln
                                                          1

ctt gta cct gat ata gag ttc aag att act tat acc cgg tct cca gat      105
Leu Val Pro Asp Ile Glu Phe Lys Ile Thr Tyr Thr Arg Ser Pro Asp
        5                  10                  15

ggt gat ggc gtt gga aac agc tac att gaa gat aat gat gat gac agc      153
Gly Asp Gly Val Gly Asn Ser Tyr Ile Glu Asp Asn Asp Asp Asp Ser
    20                  25                  30

aaa atg gca gat ctc ttg tcc tac ttc cag cag caa ctc aca ttt cag      201
Lys Met Ala Asp Leu Leu Ser Tyr Phe Gln Gln Gln Leu Thr Phe Gln
35                  40                  45                  50

gag tct gtg ctt aaa ctg tgt cag cct gag ctt gag agc agt cag att      249
Glu Ser Val Leu Lys Leu Cys Gln Pro Glu Leu Glu Ser Ser Gln Ile
                55                  60                  65

cac ata tct gtg ctg cca atg gag gtc ctg atg tac atc ttc cga tgg      297
His Ile Ser Val Leu Pro Met Glu Val Leu Met Tyr Ile Phe Arg Trp
            70                  75                  80

gtg gtg tct agt gac ctg gac ctc aga tca ttg gag cag ctg tcg ctg      345
Val Val Ser Ser Asp Leu Asp Leu Arg Ser Leu Glu Gln Leu Ser Leu
        85                  90                  95

gtg tgc aga gga ttc tac atc tgt gcc aga gac cct gaa ata tgg cgt      393
Val Cys Arg Gly Phe Tyr Ile Cys Ala Arg Asp Pro Glu Ile Trp Arg
    100                 105                 110

ctg gcc tgc ttg aaa gtt tgg ggc aga agc tgt att aaa ctt gtt ccg      441
Leu Ala Cys Leu Lys Val Trp Gly Arg Ser Cys Ile Lys Leu Val Pro
115                 120                 125                 130

tac acg tcc tgg aga gag atg ttt tta gaa cgg cct cgt gtt cgg ttt      489
Tyr Thr Ser Trp Arg Glu Met Phe Leu Glu Arg Pro Arg Val Arg Phe
                135                 140                 145

gat ggc gtg tat atc agt aaa acc aca tat att cgt caa ggg gaa cag      537
Asp Gly Val Tyr Ile Ser Lys Thr Thr Tyr Ile Arg Gln Gly Glu Gln
            150                 155                 160

tct ctt gat ggt ttc tat aga gcc tgg cac caa gtg gaa tat tac agg      585
Ser Leu Asp Gly Phe Tyr Arg Ala Trp His Gln Val Glu Tyr Tyr Arg
        165                 170                 175
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tac ata aga ttc ttt cct gat ggc cat gtg atg atg ttg aca acc cct 633
Tyr Ile Arg Phe Phe Pro Asp Gly His Val Met Met Leu Thr Thr Pro
180 185 190

gaa gag cct cag tcc att gtt cca cgt tta aga act agg aat acc agg 681
Glu Glu Pro Gln Ser Ile Val Pro Arg Leu Arg Thr Arg Asn Thr Arg
195 200 205 210

act gat gca att cta ctg ggt cac tat cgc ttg tca caa gac aca gac 729
Thr Asp Ala Ile Leu Leu Gly His Tyr Arg Leu Ser Gln Asp Thr Asp
215 220 225

aat cag acc aaa gta ttt gct gta ata act aag aaa aaa gaa gaa aaa 777
Asn Gln Thr Lys Val Phe Ala Val Ile Thr Lys Lys Lys Glu Glu Lys
230 235 240

cca ctt gac tat aaa tac aga tat ttt cgt cgt gtc cct gta caa gaa 825
Pro Leu Asp Tyr Lys Tyr Arg Tyr Phe Arg Arg Val Pro Val Gln Glu
245 250 255

gca gat cag agt ttt cat gtg ggg cta cag cta tgt tcc agt ggt cac 873
Ala Asp Gln Ser Phe His Val Gly Leu Gln Leu Cys Ser Ser Gly His
260 265 270

cag agg ttc aac aaa ctc atc tgg ata cat cat tct tgt cac att act 921
Gln Arg Phe Asn Lys Leu Ile Trp Ile His His Ser Cys His Ile Thr
275 280 285 290

tac aaa tca act ggt gag act gca gtc agt gct ttt gag att gac aag 969
Tyr Lys Ser Thr Gly Glu Thr Ala Val Ser Ala Phe Glu Ile Asp Lys
295 300 305

atg tac acc ccc ttg ttc ttc gcc aga gta agg agc tac aca gct ttc 1017
Met Tyr Thr Pro Leu Phe Phe Ala Arg Val Arg Ser Tyr Thr Ala Phe
310 315 320

tca gaa agg cct ctg tagagcctca agtccagtcc tctatcactt ttgcatgaat 1072
Ser Glu Arg Pro Leu
325

taa 1075

<210> 12
<211> 327
<212> PRT
<213> homo sapien

<400> 12
Met Gln Leu Val Pro Asp Ile Glu Phe Lys Ile Thr Tyr Thr Arg Ser
1 5 10 15
Pro Asp Gly Asp Gly Val Gly Asn Ser Tyr Ile Glu Asp Asn Asp Asp
20 25 30
Asp Ser Lys Met Ala Asp Leu Leu Ser Tyr Phe Gln Gln Gln Leu Thr
35 40 45

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Phe Gln Glu Ser Val Leu Lys Leu Cys Gln Pro Glu Leu Glu Ser Ser
    50                  55                  60
Gln Ile His Ile Ser Val Leu Pro Met Glu Val Leu Met Tyr Ile Phe
65                  70                  75                  80
Arg Trp Val Val Ser Ser Asp Leu Asp Leu Arg Ser Leu Glu Gln Leu
                85                  90                  95
Ser Leu Val Cys Arg Gly Phe Tyr Ile Cys Ala Arg Asp Pro Glu Ile
            100                 105                 110
Trp Arg Leu Ala Cys Leu Lys Val Trp Gly Arg Ser Cys Ile Lys Leu
        115                 120                 125
Val Pro Tyr Thr Ser Trp Arg Glu Met Phe Leu Glu Arg Pro Arg Val
    130                 135                 140
Arg Phe Asp Gly Val Tyr Ile Ser Lys Thr Thr Tyr Ile Arg Gln Gly
145                 150                 155                 160
Glu Gln Ser Leu Asn Gly Phe Tyr Arg Ala Trp His Gln Val Glu Tyr
                165                 170                 175
Tyr Arg Tyr Ile Arg Phe Phe Pro Asp Gly His Val Met Met Leu Thr
            180                 185                 190
Thr Pro Glu Glu Pro Gln Ser Ile Val Pro Arg Leu Arg Thr Arg Asn
        195                 200                 205
Thr Arg Thr Asp Ala Ile Leu Leu Gly His Tyr Arg Leu Ser Gln Asp
    210                 215                 220
Thr Asp Asn Gln Thr Lys Val Phe Ala Val Ile Thr Lys Lys Lys Glu
225                 230                 235                 240
Glu Lys Pro Leu Asp Tyr Lys Tyr Arg Tyr Phe Arg Arg Val Pro Val
                245                 250                 255
Gln Gln Ala Asp Gln Ser Phe His Val Gly Leu Gln Leu Cys Ser Ser
            260                 265                 270
Gly His Gln Arg Phe Asn Lys Leu Ile Trp Ile His His Ser Cys His
        275                 280                 285
Ile Thr Tyr Lys Ser Thr Gly Glu Thr Ala Val Ser Ala Phe Glu Ile
    290                 295                 300
Asp Lys Met Tyr Thr Pro Leu Phe Phe Ala Arg Val Arg Ser Tyr Thr
305                 310                 315                 320
Ala Phe Ser Glu Arg Pro Leu
                325

<210> 13
<211> 2037
<212> DNA
<213> Homo sapien

<220>
<221> CDS
<222> (70)...(1410)

<400> 13
aagcaggcag gttgctcagc tgccccggga gcggttcctc cacctgaggc agactccacg      60
tcggctggc atg agc cgg cgc ccc tgc agc tgc gcc cta cgg cca ccc cgc     111
          Met Ser Arg Arg Pro Cys Ser Cys Ala Leu Arg Pro Pro Arg
           1               5                  10

tgc tcc tgc agc gcc agc ccc agc gca gtg aca gcc gcc ggg cgc cct       159
Cys Ser Cys Ser Ala Ser Pro Ser Ala Val Thr Ala Ala Gly Arg Pro
 15                  20                  25                  30
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cga ccc tcg gat agt tgt aaa gaa gaa agt tct acc ctt tct gtc aaa      207
Arg Pro Ser Asp Ser Cys Lys Glu Glu Ser Ser Thr Leu Ser Val Lys
            35                  40                  45

atg aag tgt gac ttt aat tgt aac cat gtt cat tcc gga ctt aaa ctg      255
Met Lys Cys Asp Phe Asn Cys Asn His Val His Ser Gly Leu Lys Leu
        50                  55                  60

gta aaa cct gat gac att gga aga cta gtt tcc tac acc cct gca tat      303
Val Lys Pro Asp Asp Ile Gly Arg Leu Val Ser Tyr Thr Pro Ala Tyr
    65                  70                  75

ttg gaa ggt tcc tgt aaa gac tgc att aaa gac tat gaa agg ctg tca      351
Leu Glu Gly Ser Cys Lys Asp Cys Ile Lys Asp Tyr Glu Arg Leu Ser
80                  85                  90

tgt att ggg tca ccg att gtg agc cct agg att gta aaa ctt gaa act      399
Cys Ile Gly Ser Pro Ile Val Ser Pro Arg Ile Val Lys Leu Glu Thr
95                  100                 105                 110

gaa agc aag cgc ttg cat aac aag gaa aat caa cat gtg caa cag aca      447
Glu Ser Lys Arg Leu His Asn Lys Glu Asn Gln His Val Gln Gln Thr
                115                 120                 125

ctt aat agt aca aat gaa ata gaa gca cta gag acc agt aga ctt tat      495
Leu Asn Ser Thr Asn Glu Ile Glu Ala Leu Glu Thr Ser Arg Leu Tyr
            130                 135                 140

gaa gac agt ggc tat tcc tca ttt tct cta caa agt ggc ctc agt gaa      543
Glu Asp Ser Gly Tyr Ser Ser Phe Ser Leu Gln Ser Gly Leu Ser Glu
        145                 150                 155

cat gaa gaa ggt acc ctc ctg gag gag aat ttt ggt gac agt cta caa      591
His Glu Glu Gly Thr Leu Leu Glu Glu Asn Phe Gly Asp Ser Leu Gln
    160                 165                 170

tcc tgc ctg cta caa ata caa agc cca gac caa tat ccc aac aaa aac      639
Ser Cys Leu Leu Gln Ile Gln Ser Pro Asp Gln Tyr Pro Asn Lys Asn
175                 180                 185                 190

ttg ctg cca gtt ctt cat ttt gaa aaa gtg gtt tgt tca aca tta aaa      687
Leu Leu Pro Val Leu His Phe Glu Lys Val Val Cys Ser Thr Leu Lys
                195                 200                 205

aag aat gca aaa cga aat cct aaa gta gat cgg gag atg ctg aag gaa      735
Lys Asn Ala Lys Arg Asn Pro Lys Val Asp Arg Glu Met Leu Lys Glu
            210                 215                 220

att ata gcc aga gga aat ttt aga ctg cag aat ata att ggc aga aaa      783
Ile Ile Ala Arg Gly Asn Phe Arg Leu Gln Asn Ile Ile Gly Arg Lys
        225                 230                 235

atg ggc cta gaa tgt gta gat att ctc agc gaa ctc ttt cga agg gga      831
Met Gly Leu Glu Cys Val Asp Ile Leu Ser Glu Leu Phe Arg Arg Gly
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240 245 250

ctc aga cat gtc tta gca act att tta gca caa ctc agt gac atg gac 879
Leu Arg His Val Leu Ala Thr Ile Leu Ala Gln Leu Ser Asp Met Asp
255 260 265 270

tta atc aat gtg tct aaa gtg agc aca act tgg aag aag atc cta gaa 927
Leu Ile Asn Val Ser Lys Val Ser Thr Thr Trp Lys Lys Ile Leu Glu
275 280 285

gat gat aag ggg gca ttc cag ttg tac agt aaa gca atc caa aga gtt 975
Asp Asp Lys Gly Ala Phe Gln Leu Tyr Ser Lys Ala Ile Gln Arg Val
290 295 300

acc gaa aac aac aat aaa ttt tca cct cat gct tca acc aga gaa tat 1023
Thr Glu Asn Asn Asn Lys Phe Ser Pro His Ala Ser Thr Arg Glu Tyr
305 310 315

gtt atg ttc aga acc cca ctg gct tct gtt cag aaa tca gca gcc cag 1071
Val Met Phe Arg Thr Pro Leu Ala Ser Val Gln Lys Ser Ala Ala Gln
320 325 330

act tct ctc aaa aaa gat gct caa acc aag tta tcc aat caa ggt gat 1119
Thr Ser Leu Lys Lys Asp Ala Gln Thr Lys Leu Ser Asn Gln Gly Asp
335 340 345 350

cag aaa ggt tct act tat agt cga cac aat gaa ttc tct gag gtt gcc 1167
Gln Lys Gly Ser Thr Tyr Ser Arg His Asn Glu Phe Ser Glu Val Ala
355 360 365

aag aca ttg aaa aag aac gaa agc ctc aaa gcc tgt att cgc tgt aat 1215
Lys Thr Leu Lys Lys Asn Glu Ser Leu Lys Ala Cys Ile Arg Cys Asn
370 375 380

tca cct gca aaa tat gat tgc tat tta caa cgg gca acc tgc aaa cga 1263
Ser Pro Ala Lys Tyr Asp Cys Tyr Leu Gln Arg Ala Thr Cys Lys Arg
385 390 395

gaa ggc tgt gga ttt gat tat tgt acg aag tgt ctc tgt aat tat cat 1311
Glu Gly Cys Gly Phe Asp Tyr Cys Thr Lys Cys Leu Cys Asn Tyr His
400 405 410

act acc aaa gac tgt tca gat ggc aag ctc ctc aaa gcc agt tgt aaa 1359
Thr Thr Lys Asp Cys Ser Asp Gly Lys Leu Leu Lys Ala Ser Cys Lys
415 420 425 430

ata ggt ccc ctg cct ggt aca aag aaa agc aaa aag aat tta cga aga 1407
Ile Gly Pro Leu Pro Gly Thr Lys Lys Ser Lys Lys Asn Leu Arg Arg
435 440 445

ttg tgatctctta ttaaatcaat tgttactgat catgaatgtt agttagaaaa 1460
Leu

tgttaggttt taacttaaaa aaaattgtat tgtgattttc aatttatgtt tgaaatcggt 1520

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gtagtatcct gaggtttttt tccccccaga agataaagag gatagacaac ctcttaaaat   1580
atttttacaa tttaatgaga aaaagtttaa aattctcaat acaaatcaaa caatttaaat   1640
attttaagaa aaaaggaaaa gtagatagtg atactgaggg taaaaaaaaa ttgattcaat   1700
tttatggtaa aggaaaccca tgcaatttta cctagacagt cttaaatatg tctggttttc   1760
catctgttag catttcagac attttatgtt cctcttactc aattgatacc aacagaaata   1820
tcaacttctg gagtctatta aatgtgttgt cacctttcta aagctttttt tcattgtgtg   1880
tatttcccaa gaaagtatcc tttgtaaaaa cttgcttgtt ttccttattt ctgaaatctg   1940
ttttaatatt tttgtataca tgtaaatatt tctgtatttt ttatatgtca aagaatatgt   2000
ctcttgtatg tacatataaa aataaatttt gctcaat                            2037

<210> 14
<211> 447
<212> PRT
<213> Homo sapien

<400> 14
Met Ser Arg Arg Pro Cys Ser Cys Ala Leu Arg Pro Pro Arg Cys Ser
 1               5                  10                  15
Cys Ser Ala Ser Pro Ser Ala Val Thr Ala Ala Gly Arg Pro Arg Pro
            20                  25                  30
Ser Asp Ser Cys Lys Glu Glu Ser Ser Thr Leu Ser Val Lys Met Lys
        35                  40                  45
Cys Asp Phe Asn Cys Asn His Val His Ser Gly Leu Lys Leu Val Lys
    50                  55                  60
Pro Asp Asp Ile Gly Arg Leu Val Ser Tyr Thr Pro Ala Tyr Leu Glu
65                  70                  75                  80
Gly Ser Cys Lys Asp Cys Ile Lys Asp Tyr Glu Arg Leu Ser Cys Ile
                85                  90                  95
Gly Ser Pro Ile Val Ser Pro Arg Ile Val Lys Leu Glu Thr Glu Ser
            100                 105                 110
Lys Arg Leu His Asn Lys Glu Asn Gln His Val Gln Gln Thr Leu Asn
        115                 120                 125
Ser Thr Asn Glu Ile Glu Ala Leu Glu Thr Ser Arg Leu Tyr Glu Asp
    130                 135                 140
Ser Gly Tyr Ser Ser Phe Ser Leu Gln Ser Gly Leu Ser Glu His Glu
145                 150                 155                 160
Glu Gly Thr Leu Leu Glu Glu Asn Phe Gly Asp Ser Leu Gln Ser Cys
                165                 170                 175
Leu Leu Gln Ile Gln Ser Pro Asp Gln Tyr Pro Asn Lys Asn Leu Leu
            180                 185                 190
Pro Val Leu His Phe Glu Lys Val Val Cys Ser Thr Leu Lys Lys Asn
        195                 200                 205
Ala Lys Arg Asn Pro Lys Val Asp Arg Glu Met Leu Lys Glu Ile Ile
    210                 215                 220
Ala Arg Gly Asn Phe Arg Leu Gln Asn Ile Ile Gly Arg Lys Met Gly
225                 230                 235                 240
Leu Glu Cys Val Asp Ile Leu Ser Glu Leu Phe Arg Arg Gly Leu Arg
                245                 250                 255
His Val Leu Ala Thr Ile Leu Ala Gln Leu Ser Asp Met Asp Leu Ile
            260                 265                 270
Asn Val Ser Lys Val Ser Thr Thr Trp Lys Lys Ile Leu Glu Asp Asp
        275                 280                 285
Lys Gly Ala Phe Gln Leu Tyr Ser Lys Ala Ile Gln Arg Val Thr Glu
    290                 295                 300
Asn Asn Asn Lys Phe Ser Pro His Ala Ser Thr Arg Glu Tyr Val Met
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305                 310                 315                 320
Phe Arg Thr Pro Leu Ala Ser Val Gln Lys Ser Ala Ala Gln Thr Ser
                325                 330                 335
Leu Lys Lys Asp Ala Gln Thr Lys Leu Ser Asn Gln Gly Asp Gln Lys
            340                 345                 350
Gly Ser Thr Tyr Ser Arg His Asn Glu Phe Ser Glu Val Ala Lys Thr
        355                 360                 365
Leu Lys Lys Asn Glu Ser Leu Lys Ala Cys Ile Arg Cys Asn Ser Pro
    370                 375                 380
Ala Lys Tyr Asp Cys Tyr Leu Gln Arg Ala Thr Cys Lys Arg Glu Gly
385                 390                 395                 400
Cys Gly Phe Asp Tyr Cys Thr Lys Cys Leu Cys Asn Tyr His Thr Thr
                405                 410                 415
Lys Asp Cys Ser Asp Gly Lys Leu Leu Lys Ala Ser Cys Lys Ile Gly
            420                 425                 430
Pro Leu Pro Gly Thr Lys Lys Ser Lys Lys Asn Leu Arg Arg Leu
        435                 440                 445

<210> 15
<211> 20
<212> PRT
<213> Homo sapien

<400> 15
Ser Glu Ser Pro Gly Ala Leu Arg Ser Gly Ser Leu Arg Cys Ile Ser
 1               5                  10                  15
Leu Arg Ile Cys
            20

<210> 16
<211> 20
<212> PRT
<213> Homo sapien

<400> 16
Val Cys Arg Gly Arg Ile Arg Ser Gly Ser Leu Arg Cys Ile Ser Leu
 1               5                  10                  15
Arg Ile Cys Arg
            20

<210> 17
<211> 20
<212> PRT
<213> Homo sapien

<400> 17
Leu Leu Arg Leu Gly Cys Ile Arg Leu Leu Met Leu Arg Arg Gly Val
 1               5                  10                  15
Val Phe Arg Leu
            20

<210> 18
<211> 20
<212> PRT
<213> Homo sapien
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<400> 18
Val Leu Phe Leu Ser Leu Arg Phe Trp Gly Leu Asn Ile Val Val Met
1               5                   10                  15
Gly Arg Leu Leu
            20

<210> 19
<211> 20
<212> PRT
<213> Homo sapien

<400> 19
Cys Arg Ser Leu Gly Val Ile Val Gly Gly Thr Glu Ala Ala Gly Ala
1               5                   10                  15
Pro Thr Phe Ile
            20

<210> 20
<211> 20
<212> PRT
<213> Homo sapien

<400> 20
Val Leu Phe Leu Ser Leu Arg Phe Trp Gly Leu Asn Ile Val Val Met
1               5                   10                  15
Gly Arg Leu Leu
            20

<210> 21
<211> 20
<212> PRT
<213> Homo sapien

<400> 21
Trp Leu Arg Arg Gly Leu Val Gly Val Phe Phe Leu Leu Ser Arg Val
1               5                   10                  15
Met Val Gly Ile
            20

<210> 22
<211> 20
<212> PRT
<213> Homo sapien

<400> 22
Ser Leu Gly Leu Ser Val Cys Ile Gly Arg Arg Ala Gly Gly Gly Phe
1               5                   10                  15
Arg Gly Phe Gly
            20

<210> 23
<211> 20
<212> PRT
<213> Homo sapien
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<400> 23
Arg Phe Ala Leu Ser Ile Gly Val Cys Val Val Val Arg Val Gly Ile
1 5 10 15
Cys Leu Gly Met
20

<210> 24
<211> 20
<212> PRT
<213> Homo sapien

<400> 24
Ser Ala Val Leu Val Leu Val Tyr Val Ser Ala Ala Leu Arg Gly Arg
1 5 10 15
Gly Phe Gly Ile
20

<210> 25
<211> 20
<212> PRT
<213> Homo sapien

<400> 25
His Gly Gly Gly Arg Gly Ala Leu Val Ser Val Met Tyr Leu Cys Gly
1 5 10 15
Phe Ile Arg Leu
20

<210> 26
<211> 18
<212> PRT
<213> Homo sapien

<400> 26
Arg Gly Arg Val Ile Gly Met Trp Val Gly Leu Arg Cys Arg Met Phe
1 5 10 15
Leu Val

<210> 27
<211> 15
<212> PRT
<213> Homo sapien

<400> 27
Val Asp Trp Ala Val Tyr Ser Val Val Trp Arg Tyr Thr Thr Thr
1 5 10 15

<210> 28
<211> 20
<212> PRT
<213> Homo sapien

<400> 28

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Lys Thr Ser Val Ile Leu Val Trp Arg Leu Ser Leu Phe Phe Cys Leu
 1               5                  10                  15
Tyr Arg Ser Leu
            20

<210> 29
<211> 7
<212> PRT
<213> Homo sapien

<400> 29
Ala Asn Arg Cys Trp Arg Glu
 1               5

<210> 30
<211> 13
<212> PRT
<213> Homo sapien

<400> 30
Glu Gly Thr Leu Ser Lys Arg Met Trp Arg Thr His Asn
 1               5                  10

<210> 31
<211> 10
<212> PRT
<213> Homo sapien

<400> 31
Ser Trp Arg Asp Met Thr Gln Ser Gly Met
 1               5                  10

<210> 32
<211> 11
<212> PRT
<213> Homo sapien

<400> 32
Asp Val Pro Trp Gln Arg Ala Cys Ala Arg Gln
 1               5                  10

<210> 33
<211> 9
<212> PRT
<213> Homo sapien

<400> 33
Leu Glu Arg Val Ala Arg Trp Val Leu
 1               5

<210> 34
<211> 12
<212> PRT
<213> Homo sapien
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<400> 34
Val Ala Asp Val Leu Val Phe Trp Gly Tyr Val Phe
1 5 10

<210> 35
<211> 8
<212> PRT
<213> Homo sapien

<400> 35
Gly Asp Val Gly Val Phe Pro Glu
1 5

<210> 36
<211> 16
<212> PRT
<213> Homo sapien

<220>
<221> VARIANT
<222> (1)...(16)
<223> Xaa = Any Amino Acid

<400> 36
Pro Glu Met Met Leu Glu Gly Pro Lys Tyr Cys Leu Xaa Leu Xaa Glu
1 5 10 15

<210> 37
<211> 7
<212> PRT
<213> Homo sapien

<400> 37
Leu Leu Tyr Gly Ala Leu Ala
1 5

<210> 38
<211> 11
<212> PRT
<213> Homo sapien

<400> 38
Gly Ala Ile Lys Phe Ala His Glu Ser Cys Glu
1 5 10

<210> 39
<211> 5
<212> PRT
<213> Homo sapien

<400> 39
Pro Met Ala Met Asp
1 5

<210> 40

<211> 5
<212> PRT
<213> Homo sapien

<400> 40
Gln Glu Glu Glu Met
1 5

<210> 41
<211> 12
<212> PRT
<213> Homo sapien

<400> 41
Ile Ser Val Val His Gly Ile Gly Ser Asp Ser Asp
1 5 10

<210> 42
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 42
gggaattcgg acttatggca tgtaaaca 28

<210> 43
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 43
tagccaagtt gcgaatgga 19

<210> 44
<211> 35
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 44
gtgaattcat gcaacttgta cctgatatag agttc 35

<210> 45
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 45
ggactcgagg ctctacagag gcc 23

<210> 46
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 46
gatcaagctt atggcttcag aagagctaca g 31

<210> 47
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 47
gatcgaattc tccaaattcc gtgtctcctt tggcttg 37

<210> 48
<211> 36
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 48
cctctgaatt ccatatgagc gataaaatta ttcacc 36

<210> 49
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 49
gatcctcgag tagatggcca gctaggccag gtta 34